Critical Reviews in Oncology / Hematology 160 (2021) 103280

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Neoadjuvant chemotherapy in hormone receptor-positive/HER2-negative early breast cancer: When, why and what?

Rosalba Torrisi [a,*], Emilia Marrazzo [b], Elisa Agostinetto [a,c], Rita De Sanctis [a,c], Agnese Losurdo [a], Giovanna Masci [a], Corrado Tinterri [b], Armando Santoro [a,c]

[a] IRCCS Humanitas Research Hospital, Dept of Medical Oncology and Hematology Unit, via Manzoni 56, Rozzano, Milan, 20089, Italy
[b] IRCCS Humanitas Research Hospital, Breast Unit, via Manzoni 56, Rozzano, Milan, 20089, Italy
[c] Humanitas University, Department of Biomedical Sciences, Via Rita Levi Montalcini 4, Pieve Emanuele, Milan, 20090, Italy

ARTICLE INFO

Keywords:
Neoadjuvant chemotherapy
Luminal tumors
pCR
Breast-conserving surgery
Predictive factors

ABSTRACT

Indication for neoadjuvant chemotherapy (NACT) in HR+/HER2-negative tumors is controversial. Pathological complete response (pCR) rates range from 0 to 18 % while breast-conserving surgery (BCS) is achievable in up to 60 % of tumors. No pathological feature definitely predicts pCR; lobular and molecular luminal A tumors are less likely to achieve pCR although experiencing better outcomes. Luminal B subtype, high proliferation, lack of progesterone receptor, high tumor-infiltrating lymphocytes are positively associated with increased pCR rates but worse outcomes and the prognostic role of pCR is inconsistent across studies. Molecular intrinsic subtyping and genomic signatures appear as more accurate predictors of benefit from NACT, but larger studies are needed. Anthracycline and taxane-based chemotherapy remains the standard NACT; however, CDK 4/6 inhibitors and immune checkpoint inhibitors are under evaluation.

In conclusion, NACT may be proposed for luminal tumors requiring downsizing for BCS after multidisciplinary evaluation, provided that other contraindications to BCS are excluded.

1. Introduction

Neoadjuvant chemotherapy (NACT) has gained a paramount role in the treatment of early breast cancer (EBC). Formerly restricted to locally advanced inoperable breast cancer, its indication has been extended to operable breast cancer since the NSABP pivotal studies in early 2000s' and definitely established after the pooled analysis by Cortazar showing an improved outcome for patients achieving pathological complete response (pCR) (Cortazar et al., 2014).

The "old-fashion" studies included in Cortazar's analysis, which enrolled patients with all breast cancer subtypes selected only by tumor size and nodal involvement, showed a significant survival benefit mainly in patients with HER2-positive (HER2+) and triple-negative (TN) breast cancer (Cortazar et al., 2014). Subsequent neoadjuvant trials designed for "targeted" treatments and tumor subtypes confirmed the prognostic role of pCR in HER2+and TN EBC and NACT (plus targeted therapy in HER2+ tumors) has become the standard treatment for stage II–III HER2+ and TN EBC. Besides the surgical benefit, the identification of patients at a different long-term prognosis after NACT allows to tailor adjuvant treatments in these two tumor subtypes, particularly after the results of the CREATE-X and KATHERINE trials, which have demonstrated a benefit from a "salvage" therapy shift with capecitabine and T-DM1 in patients with TN and HER2-positive tumors, respectively, and residual disease after NACT (Masuda et al., 2017; von Minckwitz et al., 2019).

However, how does this evolving paradigm apply to hormone receptor-positive (HR+)/HER2-negative (HER2-) EBC?

We review evidence arising from NACT trials, either randomized and single-arm trials, and large retrospective series published in the last decade. We report results for HR+/HER2- EBC in terms of pCR, breast-conserving surgery (BCS) rate and long-term prognosis with the aim to enlighten how this evidence supports the indication of NACT in this tumor population. Potential predictive factors of response and of prognosis are reviewed, as well as the preferred treatments. Results of trials published up to early 2000s are reviewed by Torrisi (2009).

* Corresponding author.
E-mail address: rosalba.torrisi@humanitas.it (R. Torrisi).

https://doi.org/10.1016/j.critrevonc.2021.103280
Received 11 May 2020; Received in revised form 17 February 2021; Accepted 27 February 2021
Available online 2 March 2021

2. Methods

Articles from 2010 included in the present review were retrieved by searching PubMed. The primary key terms used for data retrievement were "Luminal tumors", "Luminal early breast cancer" combined with "neoadjuvant chemotherapy", "neoadjuvant CDK4/6 inhibitors", "neoadjuvant bevacizumab", "immune checkpoint inhibitors". Boolean logic (AND, OR) were applied to connect terms. Only manuscripts reporting results for the HR+/HER2- cohort separately were screened and only studies with a meaningful number of patients (at least 100) were included in the review.

3. What is the role of NACT in HR+/HER2- tumors?

3.1. The oncologist's point of view

In the 1990s' and 2000s', "old-fashion" randomized trials and single-Institution series of NACT, including a heterogeneous tumor population, reported a pCR rate in HR + BC ranging from 3 to 12 %, while the same treatments yielded a pCR rate of 17–42 % in HR- tumors. Notably, HER2 status was not always determined in those studies and so a variable proportion of more chemo-sensitive HR+/HER2 + BC may have been included in the HR + tumor cohorts, thus spuriously increasing the pCR rate in this subgroup. (Data reviewed by (Torrisi (2009))).

In the Cortazar pooled analysis of 12 randomized trials, which included approximately 12,000 patients, HR+/HER2- BC represented about 22 % of all tumors. Overall, a significant correlation with event-free survival (EFS) was shown in this population (HR = 0.49, 95 % CI: 0.33–0.71); however, this benefit was attributable mostly to poorly differentiated tumors that achieved a twofold greater pCR rate compared to G1/G2 tumors (16.2 % vs 7.5 %) (Cortazar et al., 2014).

The same findings were also reported by von Minckwitz in the analysis of seven randomized NACT trials conducted by the German Breast Group (GBG) and by AGO, which included >6000 patients, and distinguished HR+ tumors according to a immunohistochemistry (IHC)-defined intrinsic subtype in Luminal A and B, which achieved a pCR rate of 8.9 % and 15.4 %, respectively. Again, pCR was prognostic only in the latter group (von Minckwitz et al., 2012a).

The large ACOSOG Z1701 Alliance trial included 701 patients with T0–T4 node-positive (cN+) BC irrespective of tumor subtype. Overall, pCR was obtained in 27.8 % of patients with higher rates in HER2+ and TN tumors (45.1 % and 42 %, respectively), and was associated with improved 5-year BC-specific survival and 5-year overall survival (OS) (Boughey et al., 2014). In 323 patients with HR+/HER2- tumors, pCR was obtained only in 11.5 % but it was associated with improved BC-specific survival (100 % vs 78.3 %, 95 % CI: 70.4–84.3) and OS (97.1 %, 95 % CI: 80.9–99.6 vs 74.4 %, 95 % CI: 66.2–80.9; p = 0.033) compared with patients with residual disease (Boughley et al., 2017).

No prognostic role for pCR in HR+/HER2- tumors was reported in a retrospective series from a Japanese group in 417 HR +/HER2- tumors mostly represented by Luminal-A like tumors (about 85 %) (Hayashi et al., 2017). The very low rate of pCR (2% and 8% in the Luminal-A like and Luminal-B like tumors, respectively) may account for this finding. Interestingly, a change from cN + to pathological node negative after NACT (ypN0) resulted in a significantly longer disease-free survival (DFS; p = 0.004) and a trend in improved OS (p = 0.055) compared to pathologically node-positive (ypN+) (Hayashi et al., 2017).

A different prognostic role for pathological response in tumor and nodes has been reported also in the analysis of the huge US National Cancer Database, which included 20,265 women with T1–3 N0–1 tumors treated with NACT from 2010 to 2014 (Fayanju et al., 2018). In the 8244 HR +/HER2- tumors, pCR rate was 8.1 %, breast pCR was 1.1 % and node pCR was 7.1 % in cN + patients. In HR+/HER2- tumors, pCR and only-node pCR in cN + tumors (but not breast pCR) were associated with significantly improved 5-year OS (Fayanju et al., 2018).

On the other hand, despite this relatively small number of pCR, patients with HR+/HER2- tumors generally experienced an improved long-term outcome compared with patients with TN and HER2 + EBC with residual tumor. We may assume that administration of endocrine therapy works like a "salvage therapy" in HR+/HER2- tumors.

However, administration of endocrine therapy is independent from response to NACT and residual cancer extent, so different from other cancer subtypes, response to preoperative chemotherapy does not drive the choice of post-surgical treatment.

Therefore, it may be questioned what benefit may be envisaged from the oncologists' point of view in administering NACT in HR+/HER2- tumors given the low pCR rate and the lack of indication for subsequent systemic therapy.

3.2. The surgeons' point of view

The 2020 NCCN guidelines endorse the use of NACT in "all cases needing tumor downsizing and/or likely to become node-negative with preoperative systemic therapy" (NCCN, 2021).

The principal objective of a breast surgeon is to radically remove tumor causing the least esthetical and functional damage. Theoretically, therefore, whenever BCS is difficult for a unifocal BC or in cN + disease, the opportunity of performing preoperative therapy should also be considered in Luminal EBC while in case of multicentric and node-negative disease, a hypothetical response to NACT would not impact the surgical decision.

Focusing on Luminal EBC despite achieving much lower pCR rates compared to other tumor subtypes, particularly for Luminal A cancer, some series have reported appreciable BCS rates and breast surgical conversion rates (BSCR) as summarized in Table 1.

In the ACOSOG Z1701 Alliance trial, BCS rate was 34.5 % in patients with HR+/HER2- tumors and was significantly lower than that observed in other subtypes, consistently with lower pCR rate achieved in this subtype. However, it should be noticed that 38 % were T3 tumors. Axillary conversion rate (ACR) was 21 % and it was lower than in TN and HER2+ tumors (49 % and 65 %, respectively) (Boughey et al., 2014; Boughley et al., 2017).

Mamtani et al. reported ACR after NACT in 288 patients with cN + disease treated with NACT at the Memorial Sloan–Kettering Cancer Center (MSKCC). Overall, nodal pCR was 49 % but was only 21 % in the 110 HR+ /HER2- tumors vs 47 % and 82 % in TN and HER2+ tumors (Mamtani et al., 2016).

A nodal pCR of 20 % and ACR of 27.7 % was reported in the cN + tumors after NACT in the National Cancer Database, rates much lower than those achieved in TN (48 % and 55 %) and HER2 enriched (61 % and 66 %) tumors, respectively (Al-Hilli et al., 2018).

Retrospective analysis of a large Dutch database showed that increasing use of NACT led to an increased BCS rate in all tumor subtypes and tumor stages and also reached 50 % in the large cohort of HR+/HER2- tumors (n = 2237) although it was associated with a higher rate of involved margins (Spronk et al., 2019)

However, in most series, the BCS rate not always is a reliable surrogate of benefit from NACT since other factors, such as occurrence of extensive microcalcifications, unfavorable breast/tumor ratio, surgeon's experience and attitude, *BRCA* mutation carrier status and last, but not least, patient preference might affect surgical indication, irrespective of response to NACT.

Hage et al. retrospectively reviewed pCR, BCS and BSCR after NACT in patients treated at the Michigan University Cancer Center (Hage et al., 2017). In HR+/HER2- G1/2 and HR+/HER2- G3 tumors defined as Luminal A and B pCR rate was 6 % and 13 % and BCS was 31 % and 38 %, respectively. The Authors claimed that BCS might not reflect the true benefit of NACT because of other factors affecting surgery and excluding these cases reported a fairly higher BSCR of 54 % and 66 % in Luminal A and B tumors, respectively (Hage et al., 2017).

In the Dutch series reported by Straver et al., a BSCR of 39 % was observed in the 108HR++/HER2- tumors who had indication for

Table 1
Pathological complete response, breast- conserving surgery and axillary conversion rates in series of patients HR + veHER2 negative treated with NACT.

Study (year)	N pts/ HR+HER2-	Stage	pCR rate / pN0 %	BCS rate %/ BSCR rate%	Axillay Conversion rate%
Straver (Straver et al., 2010a)	254/140	T2 = 59 % N+ = 67 %	2%	51 %/39 %	NR
ACOSOG Z1071 (Boughey et al., 2014)	701/317	T2-T4 = 93 % N+ = 100 %	11.5 %/ 21.1 %	34.5 %/NR	21.1 %
Mamtani A (Mamtani et al., 2016)	288/110	II-III N+ = 100 %	4%/ 21 %	NR	21 %
Hage (Hage et al., 2017)	289/ 93	T2 = 60 % N+ = 69 %	6% (Lum A) 13 % (Lum B)	31 % (lum A)/54 % 38 % (lum B) 66 %	NR
Petruolo (Petruolo et al., 2017)	402	T3/4 = 54 % N+ = 75 %	7%/ 15 % *	24 %/ 46 %	15 %
Al-Hilli (Al-Hilli et al., 2018)	36,715/ 13,982	T2 = 50 % N+ = 48 %	NR/20.2 %*	NR	27.7 %
Kim (Kim et al., 2019)	244/114	T2 = 52 % T3/4 = 39 % N+ 100 %	7.9 %/22.8	38.6/ 16.3	22.8

pCR = pathological complete response; BCS = breast- conserving surgery; BSCR = breast surgical conversion rate.
NR = not reported; Lum A = Luminal A; Lum B = Luminal B; *Considering only cN + tumors.

mastectomy pre-NACT, which was not different from that observed in TN and HER2+ tumors, despite significantly different pCR rates in the three groups (2 % vs 28 % vs 35 %; $p < .001$). Conversely, in lobular carcinoma (ILC) BSCR was only 20 % (Straver et al., 2010a).

Petruolo et al. reported detailed surgical procedure performed after NACT in 402 patients with HR+/HER2- tumors (Petruolo et al., 2017). Of the 239 tumors eligible for downstaging, 109 were candidates for BCS with a BSCR of 46 % after NACT but BCS was finally performed in only 57 patients (24 %). The principal reasons for performing mastectomy in downstaged tumors were patient preference and positive margins at surgery. In patients with progesterone receptor (PgR) negative or poorly differentiated tumors, BSCR was 62 %. Nodal pCR was obtained in 15 % of cN + disease (Petruolo et al., 2017). Very recently, the same Authors reported surgical outcome of 600 patients not eligible for BCS only because of large tumor size treated with NACT from 2013 to 2019 at the MSKCC. Although HR+/HER2- status was independently associated with lower likelihood of BCS, 62 % of the 196 patients with HR+/HER2- tumors were candidates for BCS after treatment (Petruolo et al., 2020)

A Korean series recently reported 114 patients with Luminal node-positive EBC obtaining a pCR of 7.9 %, which was significantly lower than that reported in other tumor subtypes (20.8 %; $p < 0.05$) as was node pCR (22.8 % vs 40.8 %; $p < .01$). However, in Luminal EBC, BCS and BCSR were 38.6 % and 16.3 %, respectively, which were not different from those obtained in the HER2+ and TN groups. The Authors, however, acknowledged several limitations of their study as the possible bias in determining BSCR, since information on surgery pre-NACT were not available for all patients, and the lack of trastuzumab treatment for HER2+ tumors that might account for the relatively low pCR, BCS and BSCR observed in this group (Kim et al., 2019)

Another main topic involved in surgical decision process is locoregional recurrence risk after NACT.

In a pooled analysis including 10,075 patients with primary BC after NACT, Gustavo et al. clearly showed how prediction of loco regional relapse to NACT depended not only on tumor subtype but also on age, clinical nodal status, tumor grade and, more importantly, on pCR (Gustavo Werutsky et al., 2020). A very relevant fact in this report is that surgery type was not a significant independent predictor of locoregional recurrence as the first event after NACT. It is consequential that a pre-operative correct assessment can play a key role in the decision-making process before primary treatment (Gustavo Werutsky et al., 2020).

It is well known that sensitivity and specificity values of magnetic resonance imaging (MRI) of the breast are very variable between subtypes. In a study by Pasquero et al. comparing MRI between different subtypes during NACT in the evaluation of initial diagnosis and of BC response to treatments, showed that MRI has a very low specificity in predicting pCR in Luminal tumors. Therefore, in this subgroup, surgical strategy cannot rely only on MRI data, giving more importance to mammography, tomosynthesis and ultrasound imaging (Pasquero et al., 2020). Nevertheless, MRI specificity was higher (81 %) in the HER2+ subgroup than in the Luminal one. On the contrary, MRI sensitivity and specificity were 50 % and 81 %, respectively, in TN group analysis. These results are in line with literature data stating MRI predicts pCR better in TN and HER2+ tumors (Lobbes et al., 2013).

An important role in the decision-making process of assigning a breast conservative treatment or mastectomy is also the need to investigate whether current recommendations for post-mastectomy radiotherapy are applied after NACT, considering baseline clinicopathological factors and pCR status. Therefore, the decision-making process when candidating a patient with an operable HR+/HER2- EBC to NACT is quite complex and must rely on several factors other than the likelihood of achieving pCR and should be faced with a multidisciplinary approach.

4. Predictive and prognostic factors

Is it possible to predict the likelihood of benefit from NACT in patients with HR+/HER2- tumors?

What are clinical, pathological or molecular features that are associated with pCR and/or improved outcome after NACT?

4.1. Hormone receptor status

While HR status (positive vs negative) represents an established predictive factor of pCR, the association between HR quantitative expression and response has been less studied (Brouckaert et al., 2013).

Colleoni et al. investigated the association between the degree of expression of estrogen receptor (ER) and PgR and response in a large retrospective series of 533 patients treated with NACT at the same Institution (Colleoni et al., 2009). A threshold of 50 % for both receptors was chosen to define highly endocrine responsive tumors while in incompletely responsive tumors at least one receptor was <50 %. No differences in pCR rate (0% vs 2.2 %), objective response rate (ORR) (52 % vs 63 %), DFS and OS were observed among highly and incompletely endocrine responsive tumors, but both experienced a significantly better outcome compared to HR- tumors. When ER and PgR immunoreactivity was evaluated as a continuous variable (OR for 10 % decrease in the number of positive cells both for ER and PgR) it was associated to a significantly higher probability of achieving a pCR (OR 2.14, 95 % CI: 1.25–3.66; $p = 0.0053$) (Colleoni et al., 2009).

Lips et al. examined the association between IHC features (ER, PgR, Ki67) and response to NACT in 211HR++/HER2- EBC (Lips et al.,

2012a). pCR rate was 4.3 % and was not significantly associated with any of the pathological or molecular markers. When results were evaluated according to endocrine responsiveness, using the same threshold of Colleoni, pCR rate was similar in incompletely vs highly endocrine responsive tumors (5.3 % vs 3.3 %), while breast pCR/near pCR rate was significantly higher in the former group (24.6 % vs 13.1 %; p = 0.04) (Lips et al., 2012a).

Raphael et al. showed, in a population of 117 HR+ /HER2- patients treated with NACT, a negative association between ER status assessed as a continuous variable and pCR (OR = 0.98, 95 % CI: 0.97–0.99; p < 0.0001) and a tumor size reduction ≥50 % (OR = 0.99, 95 % CI: 0.99–1.00; p = 0.027) (Lips et al., 2012a). ER levels ≥80 % and ≥60 % better discriminated the likelihood to achieve pCR or a response ≥50 %, which were obtained in 5 % and 48 % of patients, respectively. Tumor size reduction ≥50 % and a pCR were also associated with an improved relapse-free survival (pCR HR = 0.17, 95 % CI: 0.07–0.43; p = 0.0002) (Raphael et al., 2017).

Single HR+ (mostly ER-positive) tumors have a different prognosis compared to double HR + tumors – that is, tumors that are both ER- and PgR-positive, and the lack of PgR is associated to a diminished sensitivity to endocrine manipulations and worse prognosis (Bardou et al., 2003; Li et al., 2020).

In the Lips series, PgR-negative tumors were associated with a numerically higher pCR rate compared to PgR-positive tumors (7.4 % vs 2.8 %; p = 0.15), while breast pCR/near pCR rate was significantly higher in the former cohort (35.3 vs 11.7 %; p < 001) (Lips et al., 2012a).

Raphael et al. showed in the same series of 117 HR+ /HER2- patients that patients with double HR + disease were less likely to achieve pCR compared to single HR + tumors (OR = 0.086; 95 % CI: 0.03–0.24; p < 0.0001) while no association with long-term outcome was observed (Raphael et al., 2018).

Van Mackelenbergh reviewed 10 neoadjuvant trials from German Breast Group and identified 5613 patients with HR + tumors, 1172 of whom had PgR-negative tumors (Raphael et al., 2018). PgR-negative tumors were more significantly poorly differentiated, HER2+ and associated with nodal involvement. In the HER2- cohort, tumors lacking PgR achieved significantly higher pCR rates compared to double HR + tumors (11.2 % vs 5.8 %, respectively, p < 0.001). Lack of PgR was an independent predictive factor of pCR in multivariate analysis either overall and in the HER2- cohort (OR 1.76; p < 0.001). Moreover, PgR was an independent prognostic factor of DFS, distant DFS and OS with a HR of 1.58 (95 % CI: 1.306–1.912; p < 0.001), HR = 1.59 (95 % CI: 1.299–1.95; p < 0.001), and HR = 1.80 (95 % CI: 1.406–2.308; p < 0.001), respectively (van Mackelenbergh et al., 2018).

In conclusion, the lack of PgR and ER <50 % appear to predict a higher likelihood of achieving pCR but are associated with worse long-term outcome.

4.2. Ki67

Despite concerns about its reproducibility, Ki-67 is recommended as a valuable factor to distinguish between Luminal A- and B-like tumors and, hence, chemotherapy benefit (Polley et al., 2013; Penault-Llorca and Radosevic-Robin, 2017).

Efforts have been performed to define its role as predictive factor of response to NACT. Despite from a tumor biological point of view, Ki67 should be viewed as a continuous variable, the identification of a threshold value predicting likelihood of pCR is appealing.

Studies reporting results after NACT according to Ki67 before 2010 are reviewed by (Yerushalmi et al. (2010)). Ki67 was unevenly associated with pCR rate and ORR and sparsely demonstrated as an independent predictive factor.

More recently, Fasching et al. analyzed Ki67 in core biopsies from 552 patients from a single German institution trying to assess the association between a cut-off of 13 %, chosen according to that used to distinguish between luminal A and B tumors, and pCR (Fasching et al., 2011). Among the 316 HR+/HER2- tumors, only 14 (8%) and 4 (2.9 %) with high and low Ki67, respectively, achieved a pCR. To improve the predictive value of Ki67 pCR rates were calculated for each possible Ki67 value; for HR+/HER2- tumors a value of 38 % discriminated between pCR rates of 18.9 % vs 3% (p < 0.0001) (Fasching et al., 2011).

Denkert et al. have analyzed the association between pCR and three different arbitrarily defined cut-offs of Ki67 in the GeparTrio trial (Denkert et al., 2013). Patients with HR+/HER2- tumors and Ki67 < 15 % had a pCR rate of 3.4 % vs 8.2 % and 18.5 % of patients with Ki67 > 15 % and <35 % or Ki67 > 35 %, respectively (p < 0.0005). Conversely, mean DFS and OS were significantly better in the former compared with the two latter cohorts (DFS = 7.45 vs 6.7 vs 6.29 years p = 0.04 and OS = 8.08 vs 7.41 vs 6.83 years p = 0.004) (Denkert et al., 2013).

Ki67 was associated with a pCR rate only in Luminal tumors in a small series of 121 tumors treated with NACT (Sueta et al., 2014). Patients with HR+/HER2- tumors achieving pCR had a median Ki67 value of 43 % versus 29 % in those who did not achieve pCR (p = 0.018).].

In the same study population of the GeparTrio trial, von Minckwitz et al. analyzed the prognostic role of Ki67 in residual disease in 667 patients, 437 of whom had HR+/HER2- tumors, using the same cut-offs as Denkert et al. (von Minckwitz et al., 2013). Ki67 was low in the vast majority (448, 73 %) of examined samples while 77 and 102 patients had intermediate and high Ki67 levels, respectively. Overall, patients with high post-treatment Ki67 levels showed higher risk for disease relapse (p < 0.0001) and death (p < 0.0001) compared with patients with low or intermediate Ki67 levels. Interestingly, patients with low post-treatment Ki67 levels showed a favorable outcome as patients with a pCR either in HR-positive and -negative cohorts. Patients with Ki67 decreasing from high pretreatment to low post-treatment levels or pCR showed a more sustained low relapse rate after 3 years compared with patients with baseline low or intermediate levels. Moreover, in the HR+/HER2- cohort post-treatment Ki67 also provided independent prognostic information beyond pCR (HR = 1.90, 95 % CI: 1.45–2.49) (von Minckwitz et al., 2013).

Montagna et al. assessed the prognostic role of Ki67 in residual disease in a large single Institution series of 904 patients treated with NACT (Montagna et al., 2015). A post-surgery Ki67 level <20 % was positively associated with DFS and OS compared to Ki67 ≥ 20 % especially in HR+/HER2- tumors. Differently from the study from van Mackelenbergh low PgR levels at surgery were also associated with improved outcome (Montagna et al., 2015).

On the contrary, in the retrospective analysis of 357 patients, Diaz Botero et al. Ki67 decrease below a cut-off of 15 % after NACT was not an independent prognostic factor in luminal B tumors (Diaz-Botero et al., 2016).

The change in Ki67 between pre- and post-NACT rather than a pretreatment value was associated with long-term prognosis in a series of 385 patients reported by (Matsubara et al. (2013)). pCR rate was much lower in the 106 Luminal A tumors compared to 60 luminal B tumors as defined by a Ki67 ≤ 14 %. (3.8 % vs 8.3 %), as well as the proportion of tumors with post-treatment Ki67 decrease (57.5 % vs 83.4 %) but Ki67 decrease predicted relapse-free survival only in luminal B, HER2+ and TN subtypes but not in Luminal A tumors (Matsubara et al. (2013)).

The prognostic role of Ki67 in post-treatment specimens was also investigated by Cabrera-Galeana et al. in a large series of 435 patients not achieving pCR after NACT (Cabrera-Galeana et al., 2018). The Authors found that in the entire cohort ≥1% Ki67 decrease was an independent prognostic factor of DFS and OS. In particular, in the 194 Luminal B-like tumors, the difference in median DFS and OS between patients who experienced a decrease vs no change or increase of Ki67 was statistically significant (DFS 47 months, 95 % CI: 39.7–47.6 vs DFS 36.2 months, 95 % CI: 29.2–43.3, respectively; p < .001; OS 70.7 months, 95 % CI: 66.7–74.8 vs OS 52.9 months, 95 % CI: 46.2–59.7; p < 0.0001) (Cabrera-Galeana et al., 2018).

In summary, higher Ki67 levels are associated with higher pCR rate

but also with worse outcomes. No threshold has been defined for either prediction or prognosis. Post-NACT Ki67 decrease has been associated with better outcomes in most studies.

4.3. Intrinsic subtypes

The predictive role of intrinsic molecular subtypes has been sparsely investigated in a relatively small series. In the series by Lips et al., intrinsic subtypes were determined by Nanostring in 142 patients: pCR rate was not different between Luminal A and B tumors (1.3 % vs 4.4 %; $p = 0.56$), while breast pCR/near pCR were doubled in luminal B (28.9 % vs 13.2 %) (Lips et al., 2012a).

Gluck et al. examined the association between pCR rate and the long-term outcome and either BluePrint intrinsic molecular subtypes and IHC subtypes in a series of 437 patients treated with NACT within four clinical trials (Gluck et al., 2013). pCR rates were 6% and 10 % in patients with Luminal A (90) and Luminal B (154) tumors while 5-year DFS was improved in the former group (93 % vs 74 %), respectively. In the 204HR+/HER2- tumors, pCR rate was 7% and DFS was 81 %. pCR was not associated with DFS either in the molecular and IHC defined subtypes although the molecular subtyping better identified a subgroup of Luminal A tumors with excellent prognosis despite the very low pCR rate (Gluck et al., 2013).

These findings were confirmed by Whitworth et al. who compared IHC and BluePrint classification in a series of 427 patients who were administered NACT within a clinical study (Whitworth et al., 2014). Overall, 22 % of tumors were differently classified between the genomic and IHCIHC assays. In particular 18 % of the 211 HR+/HER2negative tumors were reclassified in different subtypes. pCR rates were 2%,7% and 10 % in Luminal A, B and HR+/HER2- tumors, respectively, suggesting again that genomic assays were able to predict more accurately tumors less likely to benefit from NACT (Gluck et al., 2013). The same Authors reinforced this finding after submitting a larger series of 474 HR+/HER2- tumors to BluePrint subtyping (Whitworth et al., 2014). In total, 29 % and 53 % were classified as Luminal A and B, respectively, while 18 % were reclassified as basal type and pCR rate was significantly higher in the latter group compared to that achieved in the Luminal subtype (32 % vs 5%; $p > 0.001$). BluePrint subtyping was confirmed as an independent predictor of pCR in multivariate analysis (Whitworth et al., 2017).

Intrinsic subtyping by PAM50 was evaluated for its ability to predict response to NACT in a series of 120 HR+/HER2- tumors and results were compared with those obtained by IHC classification by Ohara et al. (Matsushita Ohara et al., 2019). A total of 24 and 16 HR + tumors were reclassified as HER2-enriched and TN, respectively. pCR rate was 1.9 % and 9.4 % vs 5.4 % and 8.9 % in PAM50 and IHC defined Luminal A and B tumors, respectively. Only PAM50 Luminal A subtype independently predicted pCR rate either in uni- and multi-variate analysis leading to the conclusion that molecular intrinsic subtyping is able to identify patients who are not candidate to NACT (Matsushita Ohara et al., 2019).

Bayraktar compared classification of intrinsic subtypes obtained by BluePrint/Mammaprint and PAM50 and response to NACT in a series of 122 tumors (Bayraktar et al., 2014). Overall, a poor correlation between the two assays in classifying tumor subtypes was shown (Bayraktar et al., 2014).

Larger series, including intrinsic IHC subtype classification, have been published.

Bonnefoi et al. analyzed the association between pCR after NACT and long-term prognosis among IHC-defined subtypes in patients treated within the EORTC 10,994/BIG 1−00 phase III trial (Bonnefoi et al., 2014). Luminal A and B subtypes were defined according to grading (G1/2 vs G3). pCR rate was 7.5 % among 459 Luminal A and 15 % in the 125 Luminal B tumors A and intrinsic subtype was a significant independent predictor of pCR. Although patients with Luminal A tumors experienced the best outcome despite the lower pCR rate, pCR was associated with EFS in all tumor subtypes (Bonnefoi et al., 2014).

Patients treated with NACT within the National Cancer Database were investigated for response according to IHC breast subtypes. In addition, in this series Luminal A and B tumors were distinguished according to grading (Haque et al., 2018). A total of 322 and 5941 tumors were classified as Luminal A and B, respectively, and achieved a pCR rate of 0.3 % and 8.3 %. However, despite the irrelevant pCR rate, patients with luminal A tumors had an ORR and BCS rate similar to those with Luminal B tumors (42 % and 38 % and 52 % and 34 %). In Luminal A tumors ORR was also associated with a better 5-year survival compared to patients with luminal B tumors (98.1 % vs 82.1 %, $p < 0.05$). Among Luminal B subtype pCR predicted improved 5-year OS. In multivariate analysis Luminal A subtype independently predicted 5-year OS (Haque et al., 2018).

Taken together beyond than confirming that the IHC and the molecular subtyping are not completely overlapping, these findings suggest that molecular assays, irrespective of the assay considered, more accurately define which luminal tumors are not likely to benefit from NACT.

4.4. Histology: the case of lobular cancer

ILC represents 10–15 % of all breast cancers, has distinct clinical, pathologic and molecular features compared to ductal carcinoma (IDC) and is associated with less chemo-sensitivity (Katz et al., 2007; Desmedt et al., 2016; Truin et al., 2012).

Despite ILC is more frequently associated with larger tumor size and extensive nodal involvement adjuvant chemotherapy does not appear to add benefit to endocrine therapy (Desmedt et al., 2016; Truin et al., 2012).

The impact of NACT on ILC has been investigated in a series of retrospective and randomized studies reviewed in (Truin et al., 2012) which reported a pCR rate ranging from 0 to 8%, much lower than those observed in IDC.

A meta-analysis of 17 studies published before 2013 compared pCR rate and BCS in 1764 patients with ILC with those of 12,645 patients with IDC (Petrelli and Barni, 2013). In ILC tumors, pCR rate ranged from 0 to 38.6 % with a pooled rate of 5.9 % vs 16.7 % in IDC tumors. The rate of BCS, reported in 13 studies, ranged from 17 to 72.5 % with a pooled rate of 35.4 % for ILC vs a pooled rate of 54.8 % for IDC tumors (Petrelli and Barni, 2013).

The independent predictive role of lobular histology for pCR and BCS was analyzed only in three studies with conflicting results.

One of the largest studies reported in the meta-analysis was the series of patients with HR tumors treated with NACT at the MD Anderson from 1990 and 2010 (Delpech et al., 2013). Among 1895 patients, 9% had ILC and were significantly less likely to achieve pCR (3.5 vs 14 %) and BCS (19 vs 34 %) compared with patients with IDC, although difference in pCR rate was not confirmed after adjustment for grading. Moreover, in multivariate analysis, histology was an independent predictor of mastectomy but not of pCR rate, and was not associated with different DFS or OS compared with the ductal counterpart, although median follow-up time was only 44 months (Delpech et al., 2013).

Lips et al. analyzed three neoadjuvant trials, which included 75 ILC, 59 HR+/HER2- and 29 Luminal A (Lips et al., 2012b). Overall pCR rates in ILC were lower than IDC (11 % vs 24 % $p = 0.008$) but in HR+/HER2- pCR rate was not different between the two histotypes. Lobular histology was also associated with lower BCS rate (33 % vs 46 % for IDC), although the difference was largely due to larger tumor size and multifocality at MRI rather than to lobular histology itself (Lips et al., 2012b).

More recently, Petruolo et al. retrospectively analyzed pCR and BCS rate in 402 patients with HR+/HER2- breast cancer submitted to NACT at the MSKCC from 2007 to 2016 (Petruolo et al., 2017). Lobular carcinoma represented 23 % of all the tumors; pCR rate was achieved only in 1% of lobular tumors vs 6% in IDC. Nodal pCR rate, as well as BSCR, were lower in lobular vs ductal carcinoma (6% vs 17 % and 16 % vs 48 %, respectively). Univariate analysis showed that ductal histology, lack

of PgR and poor differentiation were significantly and positively associated with downstaging to BCS and nodal pCR (Petruolo et al., 2017).

Similar results were reported in the retrospective series of the Netherland Cancer Registry including a total of 466 patients with ILC who received NACT compared with 3622 patients with IDC (Loibl et al., 2014). pCR rate was 4.9 % in patients with ILC and 20.2 % in patients with IDC and a reduction of tumor size after NACT was observed in 46.8 % of the patients with ILC and 65 % of the patients with IDC. BCS was feasible in 38.3 % in T2 and 10.9 % in T3 ILC, respectively, significantly lower than the 55.2 % and 19 % rates in the same IDC subgroups. Overall, mastectomy was performed in 82.2 % of ILC vs 62.5 % of IDC and at multivariate analysis lobular histology was independent predictor of mastectomy (Truin et al., 2016).

Loibl et al. investigated the outcome of ILC within nine randomized trials of NACT of the GBG (Loibl et al., 2014). Among more than 9000 patients enrolled, ILC were 11.7 %, were associated with larger tumor size and less nodal involvement and were significantly more frequently HR+/HER2negative and grade 1/2 (68.1 %) although 8.6 % of ILC were TN. pCR was observed in 6.2 % vs 17.4 % of ILC and non-lobular cancer, respectively. Among ILC, pCR rate was 4.6 % in HR/HER2- G1/2, 2.9 % in HR+/HER2- G3, 9.1 % in HR+/HER2+, 21.7 % in HR-/HER2+ and 17.5 % in TNBC subgroups, respectively, consistently lower compared to the non-ILC counterparts. However, biologically aggressive ILC especially in younger patients achieved similar pCR rates. In multivariable analysis age, HR status and subtype, independently predicted pCR in the ILC group. The rate of BCS was lower in ILC also in patients achieving pCR (72.6 % vs 83.4 % in non-ILC tumors) and histology represented an independent predictive factor for mastectomy even after adjustment for other known pathologic and clinical factors (Loibl et al., 2014).

Long-term outcome was not different among ILC and non-ILC tumors. pCR rate was not prognostic within the ILC cohort. In multivariate analysis, histology was an independent prognostic factor among non-pCR patients with patients with ILC tumors faring better, but not for patients who achieved pCR; in the ILC cohort, pCR and age were independent prognostic factors only for OS. The Authors concluded by suggesting to propose NACT only to patients with HR- ILC (Loibl et al., 2014).

Tamirisa et al. investigated the impact of NACT vs adjuvant chemotherapy (ACT) on node-positive ILC treated in the National Cancer Database (Tamirisa et al., 2019). Among 15,573 patients with cT1-T4 N + IlC 5551 received NACT (mostly patients with T3–T4 tumors). Overall, NACT resulted in a pCR rate of 3.4 %, but results were not reported separately in the HR + cohort, which, however, accounted for >90 % of tumors. NACT was also associated with a higher rate of mastectomy compared with patients treated with ACT (81.8 % vs 74.5 %, $p < 0.001$)(Tamirisa et al., 2019)In unadjusted analysis, NACT was also associated with worse 10-year survival compared to ACT (65.1 % vs 54.4 %, $p < 0.001$) and this unfavorable outcome was confirmed also after adjusting for known covariates and independently of disease stage (Tamirisa et al., 2019).

Lobular histology represents the most established adverse predictive factor for NACT for the lower chance of achieving either pCR and BCS.

4.5. Tumor-infiltrating lymphocytes (TILs)

Stromal TILs (sTILs), defined as the percentage of tumor stromal area containing a lymphocytic infiltrate have emerged as the most reproducible immune parameter scored by pathologists (Salgado et al., 2015;). HR + EBC represents the least immune infiltrated BC subtype, median infiltration of sTIL ranging between 7 and 10 %, usually higher than intratumoral TIL (1.5 and 5%). Several studies evaluated the association between lymphocytic infiltrate scored in pre-treatment core biopsies and the likelihood of responses to neoadjuvant therapies (Solinas et al., 2017; Denkert et al., 2010, 2018; Watanabe et al., 2018; Hwang et al., 2019). The largest series has been reported by Denkert et al. who analyzed six neoadjuvant trials from the GBG including 3771 patients treated with different chemotherapeutic regimens (Denkert et al., 2010). TILs were assessed according to the Working TILs group standardized methods and scored either as a continuous variable and in three categories: low (sTILs <10 %), intermediate (sTILs 11–59 %) high (sTILS ≥60 %) (Salgado et al., 2015; Denkert et al., 2010). As expected, luminal tumors had a significantly lower proportion of high sTILs compared with HER2+ and TNBC (13 % vs 19.5 and 30 %). sTILs concentrations were positively associated with pCR in all BC subtypes, with pCR rates increasing from 6% to 11 % and 28 % in the low, intermediate and high groups, respectively, in the Luminal cohort. The predictive role of sTILs was confirmed when the analysis was performed considering sTILs as a continuous variable (Denkert et al., 2010, 2018).

When sTILs were evaluated as prognostic marker an opposite behavior was observed among breast subtypes with a positive association between increasing levels of sTILs and DFS and OS for TNBC and longer DFS for HER2+ tumors while low sTIL concentrations were associated with improved OS in luminal tumors. This correlation was confirmed in multivariate analysis; a relative resistance to endocrine therapy in tumors expressing higher concentrations of TILs and immune-related genes was suggested by the Authors to explain this finding (Denkert et al., 2010, 2018).

Smaller series partially confirmed these findings (Watanabe et al., 2018; Hwang et al., 2019). Pre- and post-NACT TILs were assessed in a retrospective series of 197 patients, 91 of whom had HR+/HER- EBC. As expected, among HR+/HER2- tumors high TILs were a significant lower proportion compared to other subtypes (12.1 %) and exhibited a trend towards higher pCR rate compared to the low and intermediate group (27 % vs 6% and 7%, respectively). A decrease in high TILs was observed in post-NACT specimens (5% vs 10 %). As for the prognostic role of TILs in HR+/HER2- tumors, no correlation between pre-NACT and change between pre-and post-NACT TILs was shown while low post-NACT TILs significantly predicted improved relapse-free survival but not OS (Watanabe et al., 2018)

In a Korean study investigating TIL concentrations in pre- and post-NACT samples in different subtypes, pCR rate was higher in Luminal B lymphocytic predominant BC defined as expressing TILs >50 % although this subgroup accounted for a very small proportion of Luminal B tumors studied (9/64) (Hwang et al., 2019).

Despite the role of the immune environment in luminal tumors is still under investigation the finding of high levels of TILs constitutes a predictive factor of sensitiveness and benefit of NACT also in HR+/HER2- tumors.

4.6. Genomic signatures

Genomic signatures have gained an established role in the choice of adjuvant chemotherapy in HR/HER2- EBC (Sestak, 2019). Despite studies have shown a prognostic rather than a predictive role for genomic signatures except of Oncotype DX, the association between risk categories (Oncotype DX, Mammaprint, EndoPredict) and response to NACT has been investigated.

Pease et al. retrieved – from the National Cancer Database – patients with HR+/HER2- who had received NACT and for whom Oncotype DX was available (Pease et al., 2019). a total of 989 patients were included, 45.5 % with intermediate recurrence score (RS), 31.5 % with high RS and 23 % with low RS. Overall pCR was achieved by 42 patients (4.3 %), 2.2 % in the low RS, 1.6 % in the intermediate RS and 9.6 % in the high RS group, respectively. Patients with high RS had an OR = 4.8 (95 % CI: 2.01–11.82) at the multivariate logistic regression adjusting for tumor size, nodal status and tumor grading to achieve pCR compared to those in the intermediate group (Pease et al., 2019).

A smaller but prospective study with a design mirroring the larger TAILOR-X trial included 64 women with stage II–III HR+/HER2- EBC and Oncotype DX was performed in pretreatment biopsies (Bear et al., 2017). Patients with RS < 11 received neoadjuvant endocrine therapy (NET), patients with RS from 11 to 25 were randomized to NACT or NET

while patients with RS > 25 received NACT. The primary endpoint, proportion of patients refusing assigned treatment, was met since only 15 % rather than the expected 33 % of patients refused to receive NACT. A higher ORR was observed in the two groups receiving NACT; pCR in both breast and nodes was 21 % in the high RS group while NET obtained 8.3 % and 6% of breast pCR in the low and intermediate RS groups, respectively. Importantly, more than 70 % of the patients in the low and intermediate RS groups treated with NET achieved a successful BCS rate, a figure greater although not significantly than that obtained in the NACT groups (Bear et al., 2017).

The predictive power of the 70-gene signature was investigated on 167 breast cancers, 85 % with a poor prognosis signature (Straver et al., 2010b). Overall, pCR rate was 17 % all occurring in the poor prognosis signature group. Among the 88 h+/HER2- tumors 76 % and 24 % were classified as poor and good prognosis signature, respectively. Interestingly, in this group, only three (3%) patients achieved a pCR, another three patients a breast pCR and additional seven patients a near pCR (Straver et al., 2010b).

In the Neoadjuvant Breast Registry Symphony Trial (NBRST), 474 patients with HR+/HER2- tumors were classified according to Mammaprint and BluePrint subtyping to provide insight into the response to NET or NACT (Whitworth et al., 2017). Mammaprint classified 29 % of patient samples as low risk and 71 % as high risk and significantly predicted pCR after NACT, which was obtained in 2% and 13 %, of patients in the former and latter group, respectively. However, in multivariate analysis, only BluePrint subtyping remained an independent predictor of pCR. Interestingly, a higher rate of BCS was observed in the 69 Luminal patients receiving NET, compared to the NACT group (52 % vs 37 %) (Whitworth et al., 2017).

Prat et al. validated the predictive role of PAM50 risk of recurrence (ROR) score and intrinsic subtypes in a series of 216 HR+/HER2- tumor biopsies obtained before NACT (Prat et al., 2015). Endpoint was residual cancer burden (RCB) 0–I corresponding to a pCR/near PCR. Either the continuous ROR score (10 point increase OR = 1.261 $p < 0.05$) and luminal A subtype (OR = 0.341 $p < .05$) were significantly associated with response to NACT (Prat et al., 2015).

The predictive role of the 12-gene signature Endopredict was investigated retrospectively in a large pooled series of 553 patients with HR+/HER2- BC treated with NACT (Bertucci et al., 2014). Tumors were evenly distributed between low-risk (51 %) and high-risk (49 %) groups. Overall, pCR rate was 12 % and was significantly different in the two groups (7% vs 17 %; $p < 0.001$). The Endopredict score was the only independent predictive factor in multivariate analysis (OR = 1.13; 95 % CI: 1.04–1.24). A supervised analysis showed that many genes upregulated in the high-risk group were involved in cell cycle regulation and proliferation, features generally associated with greater chemo-sensitivity (Bertucci et al., 2014).

Soliman et al. compared Oncotype DX and Endopredict as predictors of NACT in six microarray data sets including 764 patients with HR+/HER2- tumors (Soliman et al., 2020). pCR was obtained in 8% of tumors (Soliman et al., 2020). Both signatures significantly predicted pCR but in a combined analysis only Endopredict maintained a significant association with pCR indicating that this assay had additional discriminating power (Loibl et al., 2018).

The prognostic role of a modified EPclin – that is, the combination of the 12-gene signature Endopredict and tumor size and nodal status in the residual tumor after NACT, has been investigated in 428 patients with HR+/HER2- tumors treated within the GeparTrio and GeparQuattro trials (Loibl et al., 2018). After a median follow-up of 67 months, mEPclin score was positively and significantly associated with a poorer outcome. Patients in the high-risk mEP clin group had a HR = 4.22 (95 % CI: 2.57–6.92; $p < 0.001$) and HR = 3.66 (95 % CI: 2.00–6.69; $p < 0.001$) for DFS and OS, respectively, compared to the low-risk group (Mittendorf et al., 2011). The Authors also compared the performance of mEPclin with that of CPS-EG which was specifically developed as a prognostic tool in residual disease after NACT in HR+/HER2- tumors and includes pretreatment clinical stage, ER status and grade and post-treatment pathological stage. This score distinguishes seven prognostic subgroups of patients with significantly different 5-year distant metastasis-free and BC-free survival, with a higher score associated with worse prognosis (Mittendorf et al., 2011). The group with high CPS-EG score had a significantly worse DFS (HR = 2.95; 95 % CI: 2.02–4.33; $p < 0.001$) and OS (HR = 3.70; 95 % CI: 2.29–5.99; $p < 0.001$) compared with the low-risk group. However, in a multivariate analysis, only mEPclin remained an independent prognostic factor (Loibl et al., 2018).

Table 2 summarizes predictive and prognostic factors for which univariate or multivariate analyses are reported.

5. Which therapy?

It is usually recommended that NACT should include the same treatment indicated as adjuvant therapy (Burstein et al., 2019). The majority of retrospective series and randomized trials have included different schedules of anthracyclines and taxanes but no specific comparisons have been performed in HR+/HER2- tumors.

Alternative strategies have been investigated and are reported below.

5.1. Optimizing taxane efficacy

Nab-paclitaxel has been compared with solvent-based paclitaxel either in the advanced and in the neoadjuvant setting. In particular, two neoadjuvant randomized trials (ETNA and GeparSepto) have compared the two taxanes in numerically significant cohorts of patients with HR+/HER2- tumors (Gianni et al., 2018; Untch et al., 2016, 2019).

The multicentric ETNA trial randomized 695 patients with TN and HR+/HER2-, the latter categorized as intermediate B-like and high B-like according to Ki67 levels ≤ or >20 %, to receive weekly nab-paclitaxel 125 mg/m^2 or solvent-based paclitaxel 90 mg/m^2 3 weeks on and 1 week off for four cycles, both followed by an anthracycline-based regimen for four cycles (Gianni et al., 2018). pCR was numerically higher in the nab-paclitaxel arm overall (22.5 % vs 18.6 %) and in each subtype (8.2 % vs 2% in intermediate B-like and 15.4 % vs 12 % in high B-like, respectively, and 41.3 % vs 37.3 % in TN tumors). Peripheral neuropathy was significantly more frequent in the nab-paclitaxel arm although not for grade 3 events (4.5 vs 1.8 %) (Gianni et al., 2018).

The GeparSepto randomized 1204 patients to receive nab-paclitaxel 150 mg/m^2 reduced to 125 mg/m^2 after 229 patients for unacceptable rate of grade 3 peripheral neuropathy and solvent -based paclitaxel 80 mg/m^2 3 weeks on 1 week off followed by four cycles of epirubicin plus cyclophosphamide (EC) (Untch et al., 2016). In total, 44 % of patients had HR+/HER2- tumors and in this subgroup pCR rate was 16 % and 12 % in the nab-paclitaxel and solvent-based paclitaxel arms, respectively ($p = 0.23$) (Untch et al., 2019). On the other hand, long-term outcome in terms of EFS and invasive DFS was significantly improved by nab-paclitaxel only in the HR+/HER2- cohort (HR = 0.65, 95 % CI: 0.45–0.94; $p = 0.021$ and HR = 0.67, 95 % CI: 0.47–0.96; $p = 0.030$) suggesting that nab-paclitaxel activity is exerted beyond achievement of pCR (Untch et al., 2019).

5.2. Dose-dense chemotherapy

Dose-dense (DD) chemotherapy, i.e. the administration of higher dose of drugs per cycle or standard dose with shorter intervals between cycles, has shown great efficacy as adjuvant strategy in node-positive and high-risk node-negative BC (Blondeaux et al., 2019). Despite inconsistent results in single trials a patient level meta-analysis has demonstrated approximately a 15 % decrease in disease recurrence and death risk, which was irrespective of HR status (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2019; Reinisch et al., 2016).

The DD approach has also been investigated in the neoadjuvant

Table 2
Clinical, pathological and molecular factors associated with pCR and long term outcome in HR+/HER2neg breast cancer for which univariate or multivariate analyses are reported.

Study (year)	Factor	N pts	pCR rate %	OR/ 95 % CI p value	DFS/RFS HR/95 %CI/p value	OS HR/95 %CI/p value
Colleoni (Colleoni et al., 2009)	ER levels	422	0 vs 3.3	2.14 / <.01*	NS	–
Raphael (Raphael et al., 2017)	ER levels	117	5	0.98/ <.001*	NS	
Lips (Lips et al., 2012a)	ER levels PgR Levels	211	5.3 vs 3.3 7.4 vs 2.8	NR/0.51 NR/0.15	NR	
Raphael (Raphael et al., 2018)	PgR levels	117	NR	0.086/<.001	NS	
Van Mackelenbergh (van Mackelenbergh et al., 2018)	PgR levels	3305	11.2 vs 5.8	1.76/<.001	1.58/<.001	1.8/ <.001
Fasching (Fasching et al., 2011)	Ki67 > 13 %	316	8 vs 2.9	NR/.03		
Denkert (Denkert et al., 2013)	Ki67 < 15 % > 35 %	590	3.4 vs 18.5	10.9/<.0005	1.79/.004	2.25/.005
Von Minckwitz) (von Minckwitz et al., 2013)	Ki67 in RCB > 35 %	444	–	–	1.90 (1.45–2.49)	–
Montagna (Montagna et al., 2015)	Ki67 in RCB < 20 % (from ≥20 %)	627	–	–	0.46 (0.34−0.64)	0.42 (0.27−0.72)
Whitworth (Whitworth et al., 2017)	Blueprint	474	Luminal 5% Basal 32 %	3.30 /<.01	–	–
Ohara (Matsushita Ohara et al., 2019)	PAM 50 Luminal A	124	Lum A 1.9 % Other 15.3 %	6.98/<.05	1.19/.68 (NS)	
Loibl (Loibl et al., 2014)	Lobular histology	1051	6.2 vs 17.4	1.81/<.001	1.08 / .35 (NS)	1.09/.35 (NS)
Denkert (Denkert et al., 2010, 2018)	TILs	1366	Low 6 Int 11 High 28	1.27/ <.001	0.99 (0·92–1·06)	1·09 (1·00–1·19) P<.05
Watanabe (Watanabe et al., 2018)	TILs (pre) (post)	91	Low 6 Int 7 High 27	P=.09	5.17 1.27–25.20, p <.03 ^	
Hwang (Hwang et al., 2019)	TILs	109	L um A 5 L um B 11	1.82 (1.62–2.07)**		
Pease (Pease et al., 2019)	Oncotype DX	989	L ow RS 2.2 Int RS 1.6 High RS 9.6	4.8 (2.01–11.82) ***	–	–
Prat (Prat et al., 2015)	PAM 50 ROR score* Lum A	216	NR	1.26/<.05 0.34/<.05	–	–
Bertucci (Bertucci et al., 2014)	Endopredict	553	Low 7 High 17	1.13 1.04−1.24	–	–
Loibl (Loibl et al., 2018)	EPclin in RCB	428	–	–	2.13/<.001	

pCR = pathological complete response; OR = odds ratio; DFS = disease free survival; RFS = relapse free survival; HR = hazard ratio; OS = overall survival; RCB = residual cancer burden; TILs = tumor infiltrating lymphocytes; RS = recurrence score; ROR = risk of recurrence.
^ for post TILs.
ROR = Risk of Recurrence.
* As continuous variable ** only for Luminal B tumors *** only for high RS.

setting. Results of earlier studies conducted in 2000s' were heterogeneous, some reporting no difference compared with standard regimens, while others – despite showing increased pCR rates, particularly for patients with HR- tumors for the DD regimens – led to inconsistent results for long-term outcomes (Reinisch et al., 2016; Untch et al., 2009, 2011a; Untch et al., 2011b). The majority of these trials did not report results according to the tumor subtype so the net effect of DD treatment in the HR+/HER2- cohort is not measurable. The SWOG 012 trial investigated a different schedule of DD AC with a weekly administration of doxorucibin for 15 weeks and oral cyclophosphamide (50 mg/day) compared to standard AC. No statistical significant difference in pCR rate was observed between the standard arm and the DD arm (20.7 % vs 22.5 %) and in the HR + cohort (10.7 vs 15.3 %), which represented 49 % and 57 % of tumors in the two arms, respectively. This slight excess of less responsive HR + tumors may have affected the benefit of the DD treatment (Ellis et al., 2011). A meta-analysis of six trials, including 2232 patients, showed a 1.5-fold greater likelihood of achieving a pCR in the DD regimen, while no difference was observed in either DFS and OS. Since, in these earlier trials, information on tumor biological features was not uniformly available, analysis by tumor subtype was not performed (Petrelli et al., 2016).

The more recent Gepar-Octo trial randomized 945 patients to receive two different DD regimens whose efficacy had been established in previous trials: intense DD sequential epirubicin, paclitaxel and cyclophosphamide (iddEPC) vs weekly treatment with paclitaxel plus nonpegylated liposomal doxorubicin (PM) with additional carboplatin (PM[Cb]) in TNBC (Schneeweiss et al., 2019). A total of 160 patients had luminal B tumors defined by Ki67 > 20 %, 60 % were poorly differentiated tumors, median tumor size was 27 mm and only 13 % were node negative at ultrasound. pCR was observed in 14.1 % and 14.4 % of patients treated with iddEPC and PM, respectively, while the latter regimen was associated with an higher treatment discontinuation and non-hematological adverse event rates (Schneeweiss et al., 2019).

5.3. Chemo-endocrine therapy

Concomitant administration of chemotherapy and endocrine therapy despite a theoretical rationale is not routinely used in adjuvant treatment. Similarly, the combination has been scantily tested in the neoadjuvant setting.

The ECTO II study, a parallel, multicenter, open-label study, randomized two separate cohorts of patients with HR- and HR + tumors to receive three different chemotherapeutic regimens, including anthracyclines and taxanes ± capecitabine and associated exemestane (+GnRHa in premenopausal women) in 182 patients with HR + tumors (Zambetti et al., 2012). Approximately 70 % of tumors were up to 4 cm

and 40 % were node negative, about 20 % were HER2+; however, at that time of the study, trastuzumab was not included in the neoadjuvant treatments. In the HR + cohort, pCR in breast and nodes was obtained in 3.3 %, 13.1 % and 8.2 % in the three treatment arms, with the higher pCR rate in the capecitabine arm and BCS was feasible in 72 % of cases, a rate like that observed in the HR- cohort (81 %) despite fairly higher pCR rates in the latter group, ranging from 35.7 to 44.2% (Zambetti et al., 2012).

A total of 101 premenopausal patients with locally advanced HR + tumors treated with the combination of letrozole (plus GnRHa) and several cytotoxic regimens were retrospectively retrieved from a large single Institution database and compared in terms of pCR rate, Ki67 percetnage drop and DFS with premenopausal unmatched controls with locally advanced HR + tumors receiving only NACT and undergoing surgery at the same Institution in the same time window (Torrisi et al., 2011). Approximately two-thirds of the case population had node-positive, low ER (≤50 %) tumors and did not receive anthracycline-based regimens, while the control group received mostly anthracycline ± taxane-containing chemotherapy. pCR rate was not different (5% vs 1.1 % in case and control group, respectively), while the Ki67 decline was significantly greater in patients receiving chemo-endocrine therapy (median difference -16 vs -7; $p = 0.003$) as was greater the proportion of patients with post-treatment Ki67 < 20 %. BCS was feasible in about half of the patients in both groups. Surprisingly, 5-year DFS was significantly better in the chemo-endocrine group (78 % vs and 41 % in the control group who received tamoxifen and GnRHa after surgery [adjusted HR = 0.46, 95 % CI: 0.27–0.79; $p < 0.005$] (Torrisi et al., 2011).

Despite these intriguing findings, the nonrandomized and retrospective design has limited the implementation of these results, which were partially confirmed by a randomized study investigating the combination of preoperative letrozole (+GnRHa if premenopausal) and sequential anthracycline and taxane chemotherapy versus the same chemotherapy (Ke-Da et al., 2019). Approximately two-thirds of the patients were premenopausal, mostly cN + and equally distributed between stage II and III. Clinical response, but not pCR, rate was significantly greater in the chemo-endocrine group (84.8 % vs 72.6 %; $p = 0.019$ and 7.2 % vs 4.0 %; p = ns). In addition, final Ki67 was significantly lower and absolute Ki67 change was higher in the combination group. No difference in long-term outcome except for a trend favouring the combination arm in patients with higher baseline Ki67 was reported, which was different to the nonrandomized study (Ke-Da et al., 2019).

5.4. What about CDK 4/6 kinase inhibitors?

The combination of endocrine therapy and CDK 4/6 inhibitors has established as the gold standard for treatment of advanced luminal tumors and is under evaluation in adjuvant trials.

This combination has also been tested in the neoadjuvant setting in single-arm studies or in comparison with aromatase inhibitor alone with Ki67 decrease and clinical response rate as endpoints (Rossi et al., 2019). The largest published studies (PALLET and neoMONARCH) with the combination of letrozole and palbociclib and anastrozole and abemaciclib, respectively, have shown a significantly greater reduction of Ki67 (in 90 % and 92 % of patients with palbociclib and abemaciclib although clinical response rate was not significantly higher in the combination arm. pCR rate was reported only in the neoMONARCH and, as expected, was very low (3.7 %) (Rossi et al., 2019).

More interesting is the design of the phase II NeoPAL, which randomized 106 postmenopausal women with stage II/III PAM50 low- or intermediate-risk luminal EBC to receive a combination of letrozole and palbociclib (LETPAL) for 19 weeks versus chemotherapy with FEC 100 for three cycles followed by docetaxel for three cycles (Cottu et al., 2018). Luminal A tumors had to be node positive to be eligible. The primary endpoint was the proportion of patients with RCB 0-/I (>20 % in the statistical plan). Despite about 80 % of patients classified as high risk by PAM50, the rate of patients achieving RCB 0/I was lower than hypothesized in both groups (7.7 % vs 15.5 % in the LETPAL versus chemotherapy, respectively) with a pCR rate of 3.8 % vs 5.9 %. These results led to a premature stop of enrollment (Cottu et al., 2018). On the other hand, ultrasound response and BCS rate were comparable (55.4 % vs 53.3 % and 69.2 % vs 68.6 % in the LETPAL and chemotherapy arms, respectively) and final median Ki67 was significantly lower in the CDK 4/6 inhibitor arm (1.7 vs 3.7). Moreover, LETPAL was far better tolerated (Cottu et al., 2018).

The CORALLEEN study randomized 106 postmenopausal patients with stage I–III HR+/HER2- BC classified as luminal B by PAM50 to receive the combination of letrozole and ribociclib or chemotherapy with 4 cycles of AC followed by paclitaxel for 12 weeks (Prat et al., 2020). The duration of both treatments was 24 weeks. The principal endpoint was the proportion of patients with low ROR score in surgical samples. About 46 % of patients in both arms had a low ROR at surgery showing an activity in molecular downstaging of the tumor. On the other hand, RCB 0/I was achieved in 11.8 % vs 6.1 % in chemotherapy and letrozole plus ribociclib arm, respectively, and pCR rate was even lower (5.8 % vs 0%). Clinical response rate was higher with chemotherapy compared with letrozole plus ribociclib (78.8 % vs 57.1 %), but the proportion of BCS was similar in both groups (72.2 % vs 85.7 %) (Prat et al., 2020).

The results of these studies confirm the great efficacy of the combination of ET and CDK 4/6 inhibitors also in EBC and support the need of different endpoints to assess the activity of preoperative strategies in HR+/HER2- BC other than its optimal duration.

Recently, 3 studies on the efficacy of adjuvant CDK4/6 inhibitors have been reported with conflicting results [91–93). The MonarchE study has pointed out a significant improvement in the 2-yr invasive disease free survival (IDFS) with the addition of 2-year treatment with abemaciclib to standard adjuvant ET in high-risk HR+/HER2- EBC (Johnston et al., 2020). This finding is being questioned by the inconsistent results of the PALLAS trial, which did not show benefit from adjuvant palbociclib in a more heterogeneous population (Mayer et al., 2021). In addition,CDK 4/6 inhibitors have been also investigated as "salvage" therapy in high-risk HR+/HER2- BC in the PENELOPE-B trial conducted by the GBG. A total of 1250 patients with HR+/HER2- residual disease after NACT and CPS-EG score ≥3 or CPS-EG score > 2 and residual nodal disease were randomized to receive placebo or palbociclib 125 mg/day DD 1–21 every 28 days for 13 cycles in combination with endocrine therapy. Preliminary results presented at the last San Antonio Breast Cancer Symposium 2020] showed no benefit on IDFS from the addition of palbociclib (Loibl et al., 2020)

It is likely that in the next future CDK 4/6 inhibitors will become part of the standard adjuvant treatment of patients with high-risk HR+/HER2- EBC independently of the response to neoadjuvant chemotherapy.

5.5. Biological agents and immune checkpoint inhibitors

The anti-VEGF monoclonal antibody bevacizumab has been investigated in addition to chemotherapy in a number of neoadjuvant trials (von Minckwitz et al., 2012b; von Minckwitz et al., 2014; Bear et al., 2012, 2015; Earl et al., 2015, 2017) The largest of these trials, the GeparQuinto ran by the GBG, enrolled 1948 patients with large TNBC or cN+ HR+/HER2- tumors (von Minckwitz et al., 2012b). Patients were randomized to receive 4 cycles of EC followed by 4 cycles of docetaxel ± bevacizumab. About 65 % of patients had HR+/HER2- tumors. The addition of bevacizumab significantly increased the pCR rate from 14.9 % to 18 % ($p = 0.04$). In multivariate analysis, bevacizumab was confirmed as a significant predictor of pCR after adjustment for clinical (age, T size, nodal status) and biological (HR status, grading) factors. The addition of bevacizumab increased pCR only in TNBC treated with bevacizumab (39.3 % vs 27.9 %, $p = 0.003$) while in HR+/HER2- tumors no difference was observed between the two arms (7.7 % vs 7.8 %,

p = 1.0) (von Minckwitz et al., 2012b). Despite the relatively low pCR rate and a median tumor size of 40 mm, BCS was feasible in an appreciable rate of >60 % of patients in both treatment arms. Long-term outcome results did not show any benefit of the addition of bevacizumab in DFS and OS overall and according to tumor subtype (von Minckwitz et al., 2014).

The NSABP B-40 trial randomized 1206 patients to receive docetaxel alone or combined with capecitabine or gemcitabine for 4 cycles followed by AC for 4 cycles (Bear et al., 2012). Patients were also randomly assigned to receive bevacizumab or not for the first 6 cycles of chemotherapy and after surgery for 10 additional cycles. Consistently, with prior NSABP studies, the primary endpoint was pCR rate in the breast while pCR in breast and nodes was a secondary endpoint. Overall there was no difference in both endpoints between chemotherapy regimens, while the addition of bevacizumab increased significantly pCR rate in breast (34.5 % vs 28.2 %, p = 0.02) with a non-significant trend of pCR in breast and nodes (27.6 % vs 23 %, p = 0.08). Subtype analysis demonstrated a significant benefit of bevacizumab in HR + tumors (pCR in breast 23.2 % vs 15 %, p = 0.007 and pCR rate in breast and nodes 16.8 % vs 11 %, p = 0.03 in bevacizumab vs no bevacizumab, respectively) but not in HR- tumors. Bevacizumab increased also clinical response rate particularly in HR + tumors (62.2 % vs 50.7 %, p = 0.0003) (Loibl et al., 2020). Unlike the German study, long-term outcome analysis showed that the addition of bevacizumab significantly increased OS (HR = 0·65, 95 % CI: 0·49–0·88; p = 0.004) but not DFS (HR = 0.80, 95 % CI: 0.63–1.01; p = .06). Patients with HR + tumors seemed to derive a greater benefit from bevacizumab (DFS HR = 0.73, 95 % CI: 0.53–1·00; p = 0.05 and OS: HR = 0.63, 95 % CI: 0.42–0.96; p = 0.03), consistent with the drug's greater impact on pCR in this subset (Bear et al., 2015).

The ARTEmis trial conducted in 66 UK centers enrolled 800 patients to receive 4 cycles of bevacizumab or not in combination with 3 cycles of docetaxel followed by FEC for 3 cycles (Earl et al., 2015). The primary endpoint was breast and node pCR. HR + tumors were classified as strongly (59 %) and weakly (10 %) positive. Bevacizumab significantly increased pCR rate overall (22 % vs 17 %, p = 0.03), in HR- (45 % vs 31 %) and HR weakly positive (51 % vs 30 %) but not in HR strongly positive (7% vs 6%) tumors. However, the increased pCR rate did not translate in a reduction of mastectomy rate in the bevacizumab arm and, most importantly, was associated with a detrimental effect in patients receiving bevacizumab with a 2.99-fold increased risk of a DFS event (Earl et al., 2017).

The results of these trials are hardly comparable given the differences in tumor characteristics, chemotherapy regimens, presurgery bevacizumab cycles (4, 6 and 8 cycles) and do not allow to draw definitive conclusions. Given the higher rate of adverse events and risk of surgical complications reported in the bevacizumab arm its role in the neoadjuvant therapy of HR + BC is far from being established.

Immune checkpoint inhibitors (ICIs) have been shown to significantly increase pCR rate in early TNBC in two large randomized trials (Schmid et al., 2020; Mittendorf et al., 2020). Tumor PD-L1 expression correlates with higher tumor grading and low ER and results of ICIs in advanced luminal BC are quite discouraging with a 2.8 % of ORR in an unselected cohort with avelumab in the Javelin trial, which increased to 12 % in heavily pretreated patients with PD-L1 plus HR + tumors with pembrolizumab in the KEYNOTE-028 trial (Oner et al., 2020).

Recent studies are investigating the role of neoadjuvant ICIs also in early HR+/HER2- tumors. The I-SPY2 phase II adaptive study has shown that the addition of pembrolizumab to a standard chemotherapy sequence containing paclitaxel and anthracyclines increased the likelihood of pCR in all cancer subtypes (30 % vs 13 % in 40 HR+/HER- tumors) (Nanda et al., 2021). More recent data about neoadjuvant immunotherap from the I-SPY 2 trial, presented at 2020 American Association for Cancer Research (AACR) Virtual Meeting, evaluated the addition of durvalumab and olaparib to neoadjuvant chemotherapy in early HER2- BC. The pCR rate in patients receiving durvalumab was 37 % compared with 22 % in patients receiving chemotherapy only. Specifically, among the HR + patients, the estimated pCR rates were 28 % for the triplet regimen, versus 14 % for the controls (Pusztai et al., 2020).

The role of immunotherapy in the neoadjuvant setting for luminal BC is far from being established and is currently under investigation in a number of ongoing trials: CheckMate-7FL (NCT04109066) is evaluating the addition of nivolumab to standard neoadjuvant chemotherapy and to adjuvant endocrine treatment as well; KEYNOTE-756 (NCT03725059) is testing the addition of pembrolizumab to standard neoadjuvant chemotherapy, followed by adjuvant endocrine therapy with or without pembrolizumab; a phase IB/II study of durvalumab combined with DD EC in a neoadjuvant setting for patients with locally advanced luminal B BC is currently recruiting (NCT03356860); a phase II study of pre-operative nivolumab in combination with chemotherapy for luminal B and TNBC (separate cohorts) is ongoing (NCT03815890)

6. Discussion

The use of NACT has approximately doubled in the past decade worldwide (Spronk et al., 2019; Mougalian et al., 2015; Graham et al., 2015). If NACT is the standard strategy in all TNBC and HER2 + tumors >2 cm or cN+, the indication in HR+/HER2- tumors is much more controversial.

6.1. *Which patients should be candidates for NACT and why?*

Data reviewed in the present manuscript underline how luminal A tumors – whatever criterion is used for their definition (molecular or IHC subtyping, proliferation index, grading) – have a very low likelihood of achieving pCR (0–8 %). In Luminal B tumors, pCR rate hardly reached 15–18 % only in a few series ranging mostly about 10 % and its prognostic role, shown in large pooled analyses as Cortazar's, was only unevenly confirmed in single series. Only tumors harboring high TILs levels obtained an interesting pCR rate of 28 %, but they represent a very small subset (about 10 %) and, moreover, pCR was not associated with improved prognosis.

On the other hand, there is some evidence supporting the efficacy of NACT in increasing BCS rate also in HR+/HER2- tumors with a BSCR rate up to 50–60 %, while the rate of conversion of positive axillary nodes is much lower, not exceeding 25 %. Thus, patients with HR+/HER2- tumors needing downsizing of the primary tumor to undergo less extensive breast surgery may be proposed for NACT, while the chance of avoiding axillary dissection should not represent a true criterion for selecting patients for NACT. Ongoing studies as NEONOD2, which enroll also luminal BC patients receiving NACT for surgical downstaged axillary treatment, will help to better understand the feasibility of this procedure in routine clinical practice (Tinterri et al., 2019).

However, as underlined above, other contraindications to BCS, including patient preference, should be taken into account in the decision-making process. If BCS is the target, we should consider ORR and breast pCR or near pCR as more reliable endpoints rather than total pCR.

It is also very difficult to identify biological features that predict or negate benefit from NACT in terms of response rate and successful surgical conversion. Even in luminal A tumors, BSCR might rise to 30–50 %; therefore, it is crucial to identify additional features to select which luminal A tumors might draw benefit from NACT sparing toxicity to most patients. Lobular histology represents the most definite negative predictive factor either for pCR and BCS. Beyond histology, molecular assays defining intrinsic subtypes and genomic signatures have generally shown to more precisely and independently select luminal tumors that have no benefit from NACT. It is true that adjuvant chemotherapy is recommended in most luminal B tumors and that genomic signatures are able to better define the relative benefit of adjuvant chemotherapy in this tumor cohort. Is this paradigm applicable *tout court* to select patients for NACT? An analysis of the National Cancer Database showed that

among >1300 patients submitted to NACT only 43.9 % had a RS > 25 and would have received adjuvant chemotherapy (Kantor et al., 2019). However, one-quarter of patients had stage I BC and 30 % had a tumor ≤2 cm and, therefore, did not represent the best candidates to NACT (Kantor et al., 2019). Despite predictive role of genomic signatures in the preoperative setting has been much less extensively studied compared with the adjuvant counterpart, we may hypothesize that ideally patients with luminal tumors who are not candidates to BCS might be submitted to genomic signatures before making a decision on NACT although lack of worldwide reimbursement of these tests and their high costs represent a major drawback. Larger studies in this setting are warranted.

Biological features and molecular assays in residual disease have been inconsistently proven to be prognostic, but since no different approach than endocrine therapy can be proposed in the adjuvant setting, a true usefulness of this information is lacking presently,

The very recent ASCO Guidelines for neoadjuvant therapy, while clearly stating that neoadjuvant therapy is the treatment of choice in all but small, node-negative, TNBC, or HER2 + tumors. propose that neoadjuvant systemic therapy may be offered to reduce the extent of surgery. AS for HR+/HER2- tumors the guidelines recommend that NACT CAN be used instead of adjuvant chemotherapy in any patient in whom the chemotherapy decision can be made without surgical pathology data and/or tumor-specific genomic testing. The Guidelines also suggest that at the present time standard pathological and clinical factors as tumor stage, histology, grade and hormone receptor and HER2 status should guide the decision to pursue NACT while there is insufficient evidence to consider factors as TILs and genomic signatures (Korde et al., 2021)

6.2. *Which therapy should be preferred?*

As for the choice of therapy, apart from the role of NET in luminal A tumors, which is outside the purpose of this review, there is no evidence that treatment different from standard anthracyclines and taxanes should be preferred. Alternative strategies, although theoretically useful as combination of chemo-endocrine therapy, have been only occasionally investigated and not largely applicable. Intriguing data from studies with CDK 4/6 inhibitors represent a promise for a shifting paradigm from chemotherapy although different duration and endpoints have to be explored. Less advanced, but similarly eagerly awaited, are studies with the addition of ICIs to chemotherapy whose results, however, will probably be applicable only in selected HR+/HER2- cohorts.

For this purpose, molecular intrinsic subtyping has allowed to reclassify a proportion of immunohistochemically defined HR+/HER2- tumors in other tumor subtypes, which might benefit from different treatment approaches and strategies. We have previously described that BluePrint and PAM50 suptyping reclassified 18 % and 12.9 % IHC HR+/HER2+ tumors included in two cohorts, respectively, as basal-like. (Whitworth et al., 2017; Matsushita Ohara et al., 2019).

More recently, Bertucci et al. reclassified 5836 HR+/HER2- tumor samples into luminal (4341, 74 %), basal (931, 16 %) and HER2-enriched (564, 10 %) by BluePrint. Among the basal group, 12 % of tumors had ER < 10 %. The basal HR+/HER2- tumors reached a pCR rate of 32 % vs 9% in the luminal HR+/HER2- tumors and was similar to that observed in a control group of basal HR- tumors. More interestingly, the immune expression profiles of the two subtypes were different suggesting potential for better response ICIs for the basal HR+/HER2- subtype (Bertucci et al., 2020).

Similarly, Anurag et al., in a supervised analysis of microarray data from the ACOSOG Z1031 (Alliance) neoadjuvant aromatase inhibitor trial, identified some luminal tumors, resistant to aromatase inhibitors, with a significantly higher expression of targetable immune checkpoint components (namely IDO1, LAG3, and PD1) (Anurag et al., 2020). These findings might provide a strong rationale for selecting luminal tumors candidate to neoadjuvant trials of immunotherapy.

7. Conclusions

In conclusion, we suggest sticking with the NCCN guidelines, which recommend NACT for patients requiring tumor downsizing for breast conservation and when this goal is likely to be achieved. Unfortunately, no predictive factor is fully reliable and a complex multidisciplinary decision process should be performed case by case. For luminal B tumors, we may foresee that an extensive use of genomic signatures in the preoperative setting may help to identify patients benefitting of chemotherapy and thus better define candidates to NACT. For luminal A tumors with evidence of clinically positive nodes, who are candidate to adjuvant chemotherapy for disease burden and requiring tumor downsizing without no other contraindications for BCS, NACT might be considered. Neoadjuvant endocrine therapy should be discussed in less extended luminal A tumors and when lobular histology is present. Growing molecular and biological evidence while adding more complexity to the heterogeneous landscape of luminal tumors might also pave the way to new treatment strategies including drugs initially designed to target other tumor subtypes, such as ICI.

Declaration of Competing Interest

Rosalba Torrisi participation to Advisory Board and fees as speaker for : MSD, Pfizer, Lilly,Istituto Gentili

Armando Santoro: participation to Advisory Board and fees as speaker for: Sandoz, Servier, EISAI, Roche, Novartis, Gilead, Pfizer, BMS

Acknowledgements

Medical writing assistance was provided by Dr. Aashni Sha (Polistudium SRL, Milan Italy).

References

Al-Hilli, Z., Hoskin, T.L., Day, C.N., Habermann, E.B., Boughey, J.C., 2018. Impact of neoadjuvant chemotherapy on nodal disease and nodal surgery by tumor subtype. Ann. Surg. Oncol. 25, 482–493.

Anurag, M., Zhu, M., Huang, C., Vasaikar, S., Wang, J., Hoog, J., et al., 2020. Immune checkpoint profiles in luminal B breast Cancer. JNCI J. Natl. Cancer Inst. 112 (7) https://doi.org/10.1093/jnci/djz213.

Bardou, V.J., Arpino, G., Elledge, R.M., Osborne, C.K., Clark, G.M., 2003. Progesterone receptor status significantly improves outcome prediction over estrogen receptor status alone for adjuvant endocrine therapy in two large breast cancer databases. J. Clin. Oncol. 21, 1973–1979.

Bayraktar, S., Royce, M., Stork-Sloots, L., de Snoo, F., Gluck, S., 2014. Molecular subtyping predicts pathologic tumor response in early-stage breast cancer treated with neoadjuvant docetaxel plus capecitabine with or without trastuzumab chemotherapy. Med. Oncol. 31 (163).

Bear, H.D., Tang, G., Rastogi, P., Geyer, C.E., Robidoux, A., Atkins, J.N., et al., 2012. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. N. Engl. J. Med. 366, 310–320.

Bear, H.D., Tang, G., Rastogi, P., Geyer Jr., C.E., Liu, Q., Robidoux, A., Baez-Diaz, L., et al., 2015. Neoadjuvant plus adjuvant bevacizumab in early breast cancer (NSABP B-40 [NRG Oncology]): secondary outcomesof a phase 3, randomised controlled trial. Lancet Oncol. 16, 1037–1048.

Bear, H.D., Wan, W., Robidoux, A., et al., 2017. Using the 21- gene assay from core needle biopsies to choose neoadjuvant therapy for breast cancer. A multicenter trial. J. Surg. Oncol. 115, 917–923.

Bertucci, F., Finetti, P., Viens, P., Birnbaum, D., 2014. EndoPredict predicts for the response to neoadjuvant chemotherapy in ER-positive, HER2-negative breast cancer. Cancer Lett. 355, 70–75.

Bertucci, F., Finetti, P., Goncalves, A., Birnbaum, D., 2020. The therapeutic response of ER+/HER2− breast cancers differs according to the molecular Basal or Luminal subtype. NPJ Breast Cancer 6, 8. https://doi.org/10.1038/s41523-020-0151-5.

Blondeaux, E., Poggio, F., Del Mastro, L., 2019. Role of dose-dense chemotherapy in high-risk early breast cancer. Curr. Opin. Oncol. 31, 480–485.

Bonnefoi, H., Litière, S., Piccart, M., MacGrogan, G., Fumoleau, P., Brain, E., et al., 2014. Pathological complete response after neoadjuvant chemotherapy is an independent predictive factor irrespective of simplified breast cancer intrinsic subtypes: a landmark and two-step approach analyses from the EORTC 10994/BIG 1-00 phase III trial. Ann. Oncol. 25, 1128–1136.

Boughey, J.C., McCall, L.M., Ballman, K.V., et al., 2014. Tumor biology correlates with rates of breast-conserving surgery and pathologic complete response after neoadjuvant chemotherapy for breast cancer: findings from the ACOSOG Z1071 (Alliance) prospective multicenter clinical trial. Ann. Surg. 260, 608–616.

Boughley, J.C., Ballman, K.V., McCall, L.M., Mittendorf, E.A., Symmans, E.A., Julian, T. B., et al., 2017. Tumor biology and response to chemotherapy impact breast cancer-specific survival in node-positive breast cancer patients treated with neoadjuvant chemotherapy: long-term follow-up from ACOSOG Z1071 (Alliance). Ann. Surg. 266 (4), 667–676.

Brouckaert, O., Paridaens, R., Floris, G., Rakha, E., Osborne, K., Neven, P., 2013. A critical review why assessment of steroid hormone receptors in breast cancer should be quantitative. Ann. Oncol. 24, 46–53.

Burstein, H.J., Curigliano, G., Loibl, S., Dubsky, P., Gnant, M., Poortmans, P., et al., 2019. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Ann. Oncol. (30), 1541–1557.

Cabrera-Galeana, P., Munoz-Montano, W., Lara-Medina, F., Alvarado-Miranda, A., Perez-Sanchez, V., Villareal-Garza, C., et al., 2018. Ki67 changes identify worse outcomes in residual breast cancer tumors after neoadjuvant chemotherapy. Oncologist 23, 670–678.

Colleoni, M., Bagnardi, V., Rotmensz, N., Gelber, R.D., Viale, G., Pruneri, G., et al., 2009. Increasing steroid hormone receptors expression defines breast cancer subtypes non responsive to preoperative chemotherapy. Breast Cancer Res. Treat. 116, 359–369.

Cortazar, P., Zhang, L., Untch, M., Mehta, K., Costantino, J.P., Wolmark, N., et al., 2014. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 384, 164–172.

Cottu, P., D'Hondt, V., Dureau, S., Lerebours, F., Desmoulins, I., Heudel, P.E., et al., 2018. Letrozole and palbociclib versus chemotherapy as neoadjuvant therapy of high-risk luminal breast cancer. Ann. Oncol. 29, 2334–2340.

Delpech, Y., Coutant, C., Hsu, L., Barranger, E., Iwamoto, T., Barcenas, C.H., et al., 2013. Clinical benefit from neoadjuvant chemotherapy in oestrogen receptor-positive invasive ductal and lobular carcinomas. Br. J. Cancer 108, 285–291.

Denkert, C., Loibl, S., Noske, A., Roller, M., Mu ller, B.M., Komor, M., et al., 2010. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J. Clin. Oncol. 28, 105–113.

Denkert, C., Loibl, S., Müller, B.M., Eidtmann, H., Schmitt, W.D., Eiermann, W., et al., 2013. Ki67 levels as predictive and prognostic parameters in pretherapeutic breast cancer core biopsies: a translational investigation in the neoadjuvant GeparTrio trial. Ann. Oncol. 24, 2786–2793.

Denkert, C., von Minckwitz, G., Darb-Esfahani, S., Lederer, B., Heppner, B.I., Weber, K.E., et al., 2018. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. Lancet Oncol. 19, 40–50.

Desmedt, C., Zoppoli, G., Gundem, G., et al., 2016. Genomic characterization of primary invasive lobular breast cancer. J. Clin. Oncol. 34, 872–1881.

Diaz-Botero, S., Espinosa-Bravo, M., Rodrigues Goncalves, V., Esgueva-Colmenarejo, A., Peg, V., Perez, J., et al., 2016. Different prognostic implications of residual disease after neoadjuvant treatment: impact of ki 67 and site of response. Ann. Surg. Oncol. 23, 3831–3837.

Earl, H.M., Hiller, L., Dunn, J.A., Blenkinsop, C., Grybowicz, L., Vallier, A.-L., et al., 2015. Efficacy of neoadjuvant bevacizumab added to docetaxel followed by fl uorouracil, epirubicin, and cyclophosphamide, for women with HER2-negative early breast cancer (ARTemis): an open-label, randomised, phase 3 trial. Lancet Oncol. 16, 656–666.

Earl, H.M., Hiller, L., Dunn, J.A., Blenkinsop, C., Grybowicz, L., Vallier, A.-L., et al., 2017. Disease-free and overall survival at 3.5 years for neoadjuvant bevacizumab added to docetaxel followed by fluorouracil, epirubicin and cyclophosphamide, for women with HER2 negative early breast cancer: ARTemis Trial. Ann. Oncol. 28, 1817–1824.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2019. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet 393, 1440–1452.

Ellis, G.K., Barlow, W.E., Gralow, J.R., Hortobagyi, G.N., Russell, C.A., Royce, M.E., et al., 2011. Phase III comparison of standard doxorubicin and cyclophosphamide versus weekly doxorubicin and daily oral cyclophosphamide plus granulocyte colony-stimulating factor as neoadjuvant therapy for inflammatory and locally advanced breast cancer: SWOG 0012. J. Clin. Oncol. 29, 1014–1021.

Fasching, P.A., Heusinger, K., Haeberle, L., Niklos, M., Hein, A., Bayer, C.M., Rauh, C., Schulz-Wendtland, R., Bani, M.R., Schrauder, M., et al., 2011. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer 11 (486).

Fayanju, O.M., Ren, Y., Thomas, S.M., Greenup, R.A., Plichta, J.K., Rosenberger, L.H., et al., 2018. The clinical significance of breast-only and node-only pathologic complete response (pCR) after neoadjuvant chemotherapy (NACT). Ann. Surg. 268, 591–601.

Gianni, G., Mansutti, M., Anton, A., Calvo, L., Bisagni, G., Bermejo, B., Semiglazov, V., et al., 2018. Comparing neoadjuvant nab-paclitaxel vs paclitaxel both followed by anthracycline regimens in women with *ERBB2/HER2*-negative breast cancer—the evaluating Treatment with Neoadjuvant Abraxane (ETNA) Trial. A randomized phase 3 clinical trial. JAMA Oncol. 4, 302–308.

Gluck, S., de Snoo, H., Peeters, J., Stork-Sloots, L., Somlo, G., 2013. Molecular subtyping of early-stage breast cancer identifies a group of patients who do not benefit from neoadjuvant chemotherapy. Breast Cancer Res. Treat. 39, 759–767.

Graham, P.J., Brar, M.S., Foster, T., McCall, M., Bouchard-Fortier, A., Temple, A., et al., 2015. Neoadjuvant chemotherapy for breast cancer, is practice changing? A population-based review of current surgical trends. Ann. Surg. Oncol. 22, 3376–3382.

Gustavo Werutsky, G., Untch, M., Hanusch, C., Fasching, P.A., Blohmer, J.U., Seiler, S., et al., 2020. Locoregional recurrence risk after neoadjuvant chemotherapy: a pooled analysis of nine prospective neoadjuvant breast cancer trials. Eur. J. Cancer 130, 92–101.

Hage, N.A., Capriccioso, C., Brennan, J., Heiden, B., Zhleutin, A., Sabel, M.S., 2017. Impact of neoadjuvant chemotherapy on surgical outcomes among patients with hormone receptor positive breast cancer. J. Surg. Oncol. 116, 665–670.

Haque, W., Verma, V., Hatch, S., Suzanne Klimberg, V., Brian Butler, E., Teh, B.S., 2018. Response rates and pathologic complete response by breast cancer molecular subtype following neoadjuvant chemotherapy. Breast Cancer Res. Treat. 170 (3), 559–567.

Hayashi, N., Takahashi, Y., Matsuda, N., Tsunoda, H., Yoshida, A., Suzuki, K., et al., 2017. The prognostic effect in tumor stage and nodal status after neoadjuvant chemotherapy in each primary breast cancer subtype. Clin. Breast Cancer 18, 219–229.

Hwang, H.W., Jung, H., Hyeon, J., Park, Y.H., Ahn, J.S., Im, Y.-H., et al., 2019. A nomogram to predict pathologic complete response (pCR) and the value of tumor-infiltrating lymphocytes (TILs) for prediction of response to neoadjuvant chemotherapy (NAC) in breast cancer patients. Breast Cancer Res. Treat. 173, 255–266.

Johnston, R.D., Harbeck, N., Hegg, R., Toi, M., Martin, M., Shao, Z.M., et al., 2020. Abemaciclib combined with endocrine therapy for adjuvant treatment HR+, HER2-, node-positive, high-risk early breast cancer (monarchE). J. Clin. Oncol. https://doi.org/10.1200/JCO.20.02514.

Kantor, O., Barrera, E., Kopkash, K., Pesce, C., Barrera, E., Winchester, D.J., et al., 2019. Are we overtreating hormone receptor positive breast cancer with neoadjuvant chemotherapy? Role of OncotypeDx for hormone receptor positive patients undergoing neoadjuvant chemotherapy. Ann. Surg. Oncol. 26, 3232–3239.

Katz, A., Saad, E.S., Porter, P., Pusztai, L., 2007. Primary systemic chemotherapy of invasive lobular carcinoma of the breast. Lancet Oncol. 8, 55–62.

Ke-Da, Y., Si-Yu, W., Guang-Yu, L., Jiong, W., Gen-Hong, D., Zhen, H., et al., 2019. Concurrent neoadjuvant chemotherapy and estrogen deprivation in patients with estrogen receptor–positive, human epidermal growth factor receptor 2–negative breast cancer (CBCSG-036): a randomized, controlled, multicenter trial. Cancer 125, 2185–2193.

Kim, H.S., Yoo, T.K., Park, W.C., Cha, B.J., 2019. Potential benefits of neoadjuvant chemotherapy in clinically node-positive luminal subtype breast cancer. J. Breast Cancer 22 (3), 412–424.

Korde, L.A., Somerfield, M.R., Carey, L.A., Crews, J.R., Denduluri, N., Huang, E.S., et al., 2021. Neoadjuvant chemotherapy, endocrine therapy and targeted therapy fro breast cancer: ASCO Guideline. J. Clin. Oncol. https://doi.org/10.1200/JCO.20.03399.

Li, Y., Yang, D., Yin, X., Zhang, X., Huang, J., Wu, Y., et al., 2020. Clinicopathological characteristics and breast cancer–specific survival of patients with single hormone receptor-positive breast cancer. JAMA Network Open. 3 (1), e1918160 doi:10.1001.

Lips, E.H., Mulder, L., de Ronde, J.J., Mandjes, I.A., Vincent, A., Peeters, Vrancken, et al., 2012a. Neoadjuvant chemotherapy in ER+ HER2- breast cancer: response prediction based on immunohistochemical and molecular characteristics. Breast Cancer Res. Treat. 131, 827–836.

Lips, E.H., Mukhtar, R.A., Yau, C., de Ronde, J.J., Livasy, C., Carey, L.A., et al., 2012b. Lobular histology and response to neoadjuvant chemotherapy in invasive breast cancer. Breast Cancer Res. Treat. https://doi.org/10.1007/s10549-012-2233-z.

Lobbes, M.B.I., Smidt, M., Tjan-Heijnen, V.C.G., Van Goethem, M., Schipper, R., Beets-Tan, R.G., Wildberger, J.E., 2013. The role of magneticresonance imaging in assessing residual disease and pathologiccomplete response in breast cancer patients receiving neoadjuvantchemotherapy: a systematic review. Insights Imaging 4, 163–175.

Loibl, S., Volz, C., Mau, C., Blohmer, J.-U., Costa, S.D., Eidtmann, H., et al., 2014. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res. Treat. 144, 153–162.

Loibl, S., Weber, K., Huober, J., Krappmann, K., Marme, F., Schem, C., et al., 2018. Risk assessment after neoadjuvant chemotherapy in luminal breast cancer using a clinicomolecular predictor. Clin. Cancer Res. 24, 3358–3365.

Loibl, S., Marmè, F., Martin, M., Untch, M., Bonnefoi, H., Kim, S.-B., et al., 2020. Phase III study of Palbociclib with endocrine therapy in hormone-receptor positive. In: HER2-Negative Primary Breast Cancer and High Relapse Risk after Neoadjuvant Chemotherapy: First Results from PENELOPE-B. San Antonio Breast Cancer Symposium.

Mamtani, A., Barrio, A.V., King, T.A., et al., 2016. How often does neoadjuvant chemotherapy avoid axillary dissection in patients with histologically confirmed nodal metastases? Results of a prospective study. Ann. Surg. Oncol. 23, 3467–3474.

Masuda, N., Lee, S.-J., Ohtani, S., Im, Y.-H., Lee, E.-S., Yokota, I., et al., 2017. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N. Engl. J. Med. 376, 2147–2159.

Matsubara, N., Mukai, H., Fujii, S., Wada, N., 2013. Different prognostic significance of Ki-67 change between pre- and post-neoadjuvant chemotherapy in various subtypes of breast cancer. Breast Cancer Res. Treat. 137, 203–212.

Matsushita Ohara, A., Naoi, Y., Shimazu, K., Kagara, N., Shimoda, M., Tanei, T., et al., 2019. PAM50 for prediction of response to neoadjuvant chemotherapy for ER-positive breast cancer. Breast Cancer Res. Treat. 173, 533–543.

Mayer, E.L., Dueck, A.C., Martin, M., Rubovzsky, G., Burstein, H.J., Bellet-Ezquerra, M., et al., 2021. Palbociclib with adjuvant endocrine therapy in- early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 22, 212–222.

Mittendorf, E.A., Jeruss, J.S., Tucker, S.L., Kolli, A., Newman, L.A., Gonzalez-Angulo, A. M., et al., 2011. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. J. Clin. Oncol. 29, 1956–1962.

Mittendorf, E.A., Zhang, H., Barrios, C.H., Saji, S., Jung, K.H., Hegg, R., et al., 2020. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet 396 (10257), 1090–1100.

Montagna, E., Bagnardi, V., Viale, G., Rotmensz, N., Sporchia, A., Cancello, G., et al., 2015. Changes in PgR and Ki-67 in residual tumour and outcome of breast cancer patients treated with neoadjuvant chemotherapy. Ann. Oncol. 26, 307–313.

Mougalian, S.S., Soulos, P.R., Killelea, B.K., Donald, R., Lannin, D.R., Abu-Khalaf, M.M., DiGiovanna, M.P., et al., 2015. Use of neoadjuvant chemotherapy for patients with stage I to III breast cancer in the United States. Cancer 121, 2544–2552.

Nanda R., Liu M.C., Yau C., Shatsky, R, Pusztai L., Wallace A., et al. Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women With Early-Stage Breast Cancer An Analysis of the Ongoing Phase 2 Adaptively Randomized I-SPY2 Trial. JAMA Oncol. doi:10.1001/jamaoncol.2019.6650.

NCCN v 3.2020 guidelines. NCCN.org.

Oner, G., Altintas, S., Canturk, Z., Tjalma, W., Van Berckelaer, C., Broeckx, G., et al., 2020. The immunologic aspects in hormone receptor positive breast cancer. Cancer Treat Res Commun. 25, 100207 https://doi.org/10.1016/j.ctarc.2020.100207.

Pasquero, G., Surace, A., Ponti, A., Bortolini, M., Tota, D., Mano, M.P., Arisio, R., Benedetto, C., 2020. Baù MG role of magnetic resonance imaging in the evaluation of breast Cancer response to neoadjuvant chemotherapy. In Vivo. 34 (March-April (2)), 909–915.

Pease, A.M., Riba, L.A., Gruner, R.A., Tung, M.N., James, T.A., 2019. Oncotype DX recurrence score as a predictor of response to neoadjuvant chemotherapy. Ann. Surg. Oncol. 26, 366–371.

Penault-Llorca, F., Radosevic-Robin, N., 2017. Ki67 assessment in breast cancer: an update. Pathology 49 (2), 166–171. @.

Petrelli, F., Barni, S., 2013. Response to neoadjuvant chemotherapy in ductal compared to lobular carcinoma of the breast: a meta-analysis of published trials including 1,764 lobular breast cancer. Breast Cancer Res. Treat. 142, 227–235.

Petrelli, F., Coinu, A., Lonati, V., Cabiddu, M., Ghilardi, M., Borgonovo, K., Barni, S., 2016. Neoadjuvant dose-dense chemotherapy for locally advanced breast cancer: a meta-analysis of published studies. Anticancer Drugs 27, 702–708.

Petruolo, O.A., Pilewskie, M., Patil, S., Barrio, A.V., Stempel, M., Wen, H.Y., Morrow, M., 2017. Standard pathologic features can be used to identify a subset of estrogen receptor-positive, HER2 negative patients likely to benefit from neoadjuvant chemotherapy. Ann. Surg. Oncol. 24, 2556–2562.

Petruolo, O., Sevilimedu, V., Giacomo Montagna, G., Tiana Le, T., Morrow, M., Barrio, A. V., 2020. How often does modern neoadjuvant chemotherapy downstage patients to breast-conserving surgery? Ann Surg Onc. https://doi.org/10.1245/s10434-020-08593-08595.

Polley, M.Y., Leung, S.C., McShane, L.M., Gao, D., Hugh, J.C., Mastropasqua, M.G., Viale, G., Zabaglo, L.A., Penault-Llorca, F., Bartlett, J.M., et al., 2013. An international Ki67 reproducibility study. J. Natl. Cancer Inst. 105, 1897–1906.

Prat, A., Galvan, P., Jimenez, B., Buckingham, W., Jeiranian, H.A., Schaper, C., et al., 2015. Prediction of response to neoadjuvant chemotherapy using core needle biopsy samples with the prosigna assay. Clin. Cancer Res. 22, 560–566.

Prat, A., Saura, C., Pascual, C., Hernando, C., Munoz, M., Parè, L., et al., 2020. Ribociclib plus letrozole versus chemotherapy for postmenopausal women with hormone receptor-positive, HER2-negative, luminal B breast cancer (CORALLEEN): an open-label, multicentre, randomised, phase 2 trial. Lancet Oncol. 21, 33–43.

Pusztai, L., et al., 2020. Evaluation of durvalumab in combination with olaparib and paclitaxel in high-risk HER2 negative stage II/III breast cancer: results from the I-SPY 2 TRIAL. In: Proceedings of the 111th Annual Meeting of the American Association for Cancer Research. 2020 June 22-24. Philadelphia (PA): AACR.

Raphael, J., Gandhi, S., Li, N., Lu, F.-I., Trudeau, M., 2017. The role of quantitative estrogen receptor status in predicting tumor response at surgery in breast cancer patients treated with neoadjuvant chemotherapy. Breast Cancer Res. Treat. 164, 285–294.

Raphael, K., Kiss, A., Nofech-Mozes, S., Trudeau, M., 2018. Clinical outcomes of single versus double hormone receptor positive breast cancer patients treated with neoadjuvant chemotherapy. Clin. Breast Cancer 18, e1381–7.

Reinisch, M., Ataseven, B., Kümmel, S., 2016. Neoadjuvant dose-dense and dose-intensified chemotherapy in breast cancer – review of the literature. Breast Care 11, 13–20.

Rossi, L., McCartney, A., Risi, E., De Santo, I., Migliaccio, I., Malorni, L., et al., 2019. Cyclin-dependent kinase 4/6 inhibitors in neoadjuvant endocrine therapy of hormone receptor-positive breast cancer. Clin. Breast Cancer.

Salgado, R., Denkert, C., Demaria, S., Sirtaine, N., Klauschen, F., Pruneri, G., et al., 2015. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann. Oncol. (26), 259–271.

Schmid, P., Cortes, J., Pusztai, L., McArthur, H., Kümmel, S., Bergh, J., et al., 2020. Pembrolizumab for early triple negative breast cancer. N. Engl. J. Med. 382 (9), 810–821.

Schneeweiss, A., Möbus, V., Tesch, H., Hanusch, C., Denkert, C., Lübbe, K., et al., 2019. Intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for neoadjuvant treatment of high-risk early breast cancer (GeparOctod GBG 84): a randomized phase III trial. Eur. J. Cancer 106, 181e192.

Sestak, I., 2019. Risk stratification in early breast cancer in premenopausal and postmenopausal women:integrating genomic assays with clinicopathological features. Curr. Opin. Oncol. 31, 29–34.

Soliman, H., Wagner, S., Flake, D.D.I.I., Robson, M., Schwartzberg, L., Sharma, P., et al., 2020. Evaluation of the 12-Gene molecular score and the 21-Gene recurrence score as predictors of response to neo-adjuvant chemotherapy in estrogen receptor-positive, HER2-negative breast cancer. Ann. Surg. Oncol. 27, 765–771.

Solinas, C., Carbognin, L., De Silva, P., Criscitiello, C., Lambertini, M., 2017. Tumor-infiltrating lymphocytes in breast cancer according to tumor subtype: current state of the art. Breast 35, 142–150.

Spronk, P.E.R., Volders, J.H., van den Tol, P., Smorenburg, C.H., Vrancken Peeters, M.J., 2019. Breast conserving therapy after neoadjuvant chemotherapy; data from the Dutch breast cancer audit. Eur. J. Surg. Oncol. 45, 110–117.

Straver, M.E., Rutgers, E.J., Rodenhuis, S., Linn, S.C., Loo, C.E., Wesseling, J., et al., 2010a. The relevance of breast cancer subtypes in the outcome of neoadjuvant chemotherapy. Ann. Surg. Oncol. 17, 2411–2418.

Straver, M.E., Glas, A.M., Hannemann, J., Wesseling, J., van de Vijver, M.J., Rutgers, E. M., et al., 2010b. The 70-gene signature as a response predictor for neoadjuvant chemotherapy in breast cancer. Breast Cancer Res. Treat. 119, 551–558.

Sueta, A., Yamamoto, Y., Hayashi, M., Yamamoto, S., Inao, T., Ibusuki, M., et al., 2014. Clinical significance of pretherapeutic Ki67 as a predictive parameter for response to neoadjuvant chemotherapy in breast cancer; is it equally useful across tumor subtypes? Surgery 155, 927–935.

Tamirisa, N., Williamson, H.V., Thomas, S.M., Westbrook, K.E., Greenup, R.A., Plichta, J. K., et al., 2019. The impact of chemotherapy sequence on survival in node-positive invasive lobular carcinoma. J. Surg. Oncol. 120, 132–141.

Tinterri, C., Canavese, G., Bruzzi, P., Dozin, B., 2019. NEONOD 2: rationale and design of a multicenter non-inferiority trial to assess the effect of axillary surgery omission on the outcome of breast cancer patients presenting only micrometastasis in the sentinel lymph node after neoadjuvant chemotherapy. Contemp. Clin. Trials Commun. 17 (100496).

Torrisi, R., 2009. Preoperative chemo- and endocrine therapy. Cancer Treat. Res. 151, 103–120.

Torrisi, R., Bagnardi, V., Rotmensz, N., Scarano, E., Iorfida, M., Veronesi, P., et al., 2011. Letrozole plus GnRH analogue as preoperative and adjuvant therapy in premenopausal women with ER positive locally advanced breast cancer. Breast Cancer Res. Treat. 126, 431–441.

Truin, W., Voogd, A.C., Vreugdenhil, G., van der Heiden-van der Loo, M., Siesling, S., Roumen, R.M., 2012. Effect of adjuvant chemotherapy in postmenopausal patients with invasive ductal versus lobular breast cancer. Ann. Oncol. 23 (11), 2859–2865.

Truin, W., Vugts, G., Roumen, R.M.H., Maaskant-Braat, A.J.G., Nieuwenhuijzen, G.A.P., van der Heiden-van der Loo, M., et al., 2016. Differences in response and surgical management with neoadjuvant chemotherapy in invasive lobular versus ductal breast cancer. Ann. Surg. Oncol. 23, 51–57.

Untch, M., Möbus, V., Kuhn, W., Muck, B.R., Thomssen, C., Bauerfeind, I., et al., 2009. Intensive dose-dense chemotherapy compared with conventionally scheduled preoperative chemotherapy for high-risk primary breast cancer. J. Clin. Oncol. 27, 1–9.

Untch, M., Jackisch, C., Schneeweiss, A., Conrad, B., Aktas, B., Denkert, C., et al., 2016. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto—GBG 69): a randomised, phase 3 trial. Lancet Oncol. 17, 345–356.

Untch, M., Jackisch, C., Schneeweiss, A., Schmatloch, S., Aktas, B., Denkert, C., et al., 2019. Nab-paclitaxel improves disease-free survival in early breast cancer: GBG 69–GeparSepto. J. Clin. Oncol. 37, 2226–2234.

Untch, M., Fasching, P.A., Konecny, G.E., von Koch, F., Conrad, U., Fett, W., et al., 2011a. Prepare trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel and CMF versus a standard-dosed epirubicin/cyclophosphamide followed by paclitaxel +/2 darbepoetin alfa in primary breast cancer - results at the time of surgery. Ann. Oncol. 22, 1988–1998.

Untch, M., von Minckwitz, G., Konecny, E., Conrad, U., Fett, W., Kurzeder, C., et al., 2011b. PREPARE trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel, and CMF versus a standard-dosed epirubicin–cyclophosphamide followed by paclitaxel with or without darbepoetin alfa in primary breast cancer—outcome on prognosis. Ann. Oncol. 22, 1999–2006.

van Mackelenbergh, Mt, Denkert, C., Nekljudova, V., Kam, T., Schem, C., Marmè, F., et al., 2018. Outcome after neoadjuvant chemotherapy in estrogen receptor positive and progesterone receptor-negative breast cancer patients: a pooled analysis of individual patient data from ten prospectively randomized controlled neoadjuvant trials. Breast Cancer Res. Treat. 167, 59–71.

von Minckwitz, G., Schmitt, W.D., Loibl, S., Muller, B.M., Blohmer, J.U., Sinn, B.V., et al., 2013. Ki67 measured after neoadjuvant chemotherapy for primary breast Cancer. Clin. Cancer Res. 19, 4521–4531.

von Minckwitz, G., Loibl, S., Untch, M., Eidtmann, H., Rezai, M., Fasching, P.A., et al., 2014. Survival after neoadjuvant chemotherapy with or without bevacizumab or everolimus for HER2-negative primary breast cancer (GBG 44–GeparQuinto). Ann. Oncol. 25, 2363–2372.

von Minckwitz, G., Huang, C.-S., Mano, M.S., Loibl, S., Mamounas, E.P., Untch, M., et al., 2019. Trastuzumab emtansine for residual invasive HER2-Positive breast Cancer. N. Engl. J. Med. 380, 617–628.

von Minckwitz, G., Untch, M., Blohmer, J.-U., Costa, S.D., Eidtmann, H., Fasching, P.A., et al., 2012a. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J. Clin. Oncol. 30, 1796–1804.

von Minckwitz, G., Eidtmann, H., Rezai, M., Fasching, P.A., Tesch, Eggemann, H.H., et al., 2012b. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N. Engl. J. Med. 366, 299–309.

Watanabe, T., Hida, A.I., Inoue, N., Imamura, M., Fujimoto, Y., Akazawa, K., et al., 2018. Abundant tumor infiltrating lymphocytes after primary systemic chemotherapy predicts poor prognosis in estrogen receptor-positive/ HER2-negative breast cancers. Breast Cancer Res. Treat. 168, 135–145.
Whitworth, P., Stork-Sloots, L., de Snoo, F.A., Richards, P., Rotkis, M., Beatty, J., et al., 2014. Chemosensitivity predicted by BluePrint 80-gene functional subtype and mammaprint in the prospective Neoadjuvant Breast Registry Symphony Trial (NBRST). Ann. Surg. Oncol. 21, 3261–3267.
Whitworth, B., Beitsch, P., Mislowsky, A., Pellicane, J.V., Nash, C., Murray, M., et al., 2017. Chemosensitivity and endocrine sensitivity in clinical luminal breast cancer patients in the prospective Neoadjuvant Breast Registry Symphony Trial (NBRST) predicted by Molecular Subtyping. Ann. Surg. Oncol. 24, 669–675.
Yerushalmi, R., Woods, R., Ravdin, P.M., Hayes, M.M., Gelmon, K., 2010. Ki67 in breast cancer: prognostic and predictive potential. Lancet Oncol. 11, 174–183.
Zambetti, M., Mansutti, M., Gomez, P., Lluch, A., Dittrich, C., Zamagni, C., et al., 2012. Pathological complete response rates following different neoadjuvant chemotherapy regimens for operable breast cancer according to ER status, in two parallel, randomized phase II trials with an adaptive study design (ECTO II). Breast Cancer Res. Treat. 132, 843–851.

Rosalba Torrisi is a medical oncologist who has focused her clinical and research activity on breast cancer. She is co-author of about 100 manuscripts published on international peer-reviewed journals.

Emilia Marrazzo, breast surgeon, from 2015 ongoing Breast Surgery Consultant to the Humanitas Research Hospital. Specialized in General Surgery. Medical areas of interest: Breast cancer surgery and Oncoplastic breast reconstructive surgery. Sentinel lymph node study. Surgery for benign breast disease.

Rita De Sanctis, MD, PhD, graduated in Medicine in 2007, then received the board certification in Medical Oncology and earned a PhD in morphogenesis and tissue engineering. She is currently involved in clinical and research work on breast cancer

Agnese Losurdo, is a medical doctor specialized in oncology (2017, University of Milan) with main interest is breast cancer and she is currently a PhD student in the Humanitas Research Hospital Laboratory of Translational Immunology carrying With a project on the characterization of the T cell infiltrate in breast cancer.

Elisa Agostinetto is a medical doctor, graduated with honours at University of Udine (Italy), and a resident in medical oncology at Humanitas Research Hospital in Milan (Italy). She is currently working as research fellow at Institute Jules Bordet in Brussels (Belgium), focusing her research activity in breast cancer.

Giovanna Masci is a specialist in medical oncology and treats breast cancer in both the adjuvant and metastatic setting. She is the author and coauthor of numerous scientific articles published in international oncology journals

Corrado Tinterri: Specialized in general surgery and plastic-reconstructive surgery. from 2008 Director of Breast Unit and Breast Surgical Department of Humanitas Research Hospital. Collaboration as Professor of Breast Surgery with the Humanitas University

Armando Santoro, Director of Cancer Center and of Medical Oncology and Hematology Department at Humanitas Research and Clinical Center, Professor of Oncology at Humanitas University. He has published more than 400 scientific papers in international peer-reviewed journals. He is, affiliated to major Scientific Societies (ASCO, AIOM, ESMO, AACR, SIE, ISG) and member of the Editorial Board of several Scientific Journals.